MEDICAL LIBRARY

DEC 28 1949

The Yale Journal of Biology and Medicine

Vol. 22, No. 2, December, 1949 New Haven, Conn.

Scope. THE YALE JOURNAL OF BIOLOGY AND MEDICINE publishes original contributions in all fields of medicine, the fields of biology that are related to medicine, and in the history and teaching of these subjects.

Mailing address. Manuscripts should be addressed to THE YALE JOURNAL OF BIOLOGY AND MEDICINE, 333 Cedar Street, New Haven 11, Connecticut, U.S.A. All manuscripts should be mailed flat.

Preparation of copy. Papers should be typed in double or triple space, with references typed in double space on a separate sheet. For the convenience of authors, as well as of the editors, certain conventions in style of citation have been adopted, as follows: References will be listed alphabetically by author and numbered consecutively. In the text they will be cited by superior number without parentheses. The order of citation of journal articles will be: author's name (surname followed by initials or forename if there is no middle initial), title of article, abbreviated title of journal, year, volume number, and first page of article. Titles of journals will be abbreviated in accordance with the style used in the *Index-Catalogue of the Surgeon General's Office.* (In case the *Index-Catalogue* is not available to an author, full titles of journals should be submitted without abbreviation.) References to books will include the author's name, the title of the book, and the place of publication, publisher, and date, followed by the page or pages containing the information to which reference is made. Authors of historical papers may use the conventional footnote style.

Lucké, Baldwin and Rea, M. H.: Studies on aneurysm. J. Am. M. Ass., 1921, *77*, 935.

Barcroft, Joseph: *The respiratory function of the blood.* Cambridge, Cambridge University Press, 1914. pp. 58-61.

Illustrations. All illustrations and tabular matter must be in finished form for the printer. Illustrations must not be larger than 8½ by 11 inches; if the original is larger, it should be photographically reduced on a glossy print. Line cuts will usually be reduced for printing to four inches or less in width. The artist should be informed of the anticipated reduction before the drawing is made. All illustrative material should have titles, and the legends should be on the material itself as well as typed on a separate sheet.

Each paper is accepted with the understanding that it is to be published exclusively in THE YALE JOURNAL OF BIOLOGY AND MEDICINE unless some other specific arrangement has been made in advance.

Costs chargeable to authors. The number of free illustrations will vary with the length of the paper, but usually only two pages of halftones will be allowed free. Costs for additional halftones will be charged to the author. Special typography, including tables and formulas, in excess of 10 per cent of composition costs are chargeable to the author. Corrections in galley proof in excess of 5 per cent of original composition costs will also be charged to the author. Page proof will not normally be sent to the author, but in the event that an author makes any changes from copy after galley proof has been submitted, the entire cost will be charged to him.

Subscriptions. THE YALE JOURNAL OF BIOLOGY AND MEDICINE is published in October, December, January, March, May, and July from 333 Cedar Street, New Haven 11, Connecticut, U.S.A. The subscription price for one volume of six issues is $6.00 in the United States, $7.50 in other countries. For students registered in any school of Yale University, the subscription price is $4.00 per volume. Single copies are $1.50 each except for special issues.

Entered as second-class matter January 11, 1929, at the post office at New Haven, Connecticut, under the Act of March 3, 1879.

Copyright 1949, by THE YALE JOURNAL OF BIOLOGY AND MEDICINE, INC.

REMARKS TO UNDERGRADUATE STUDENTS OF CLINICAL MEDICINE

GROVER F. POWERS

For a few minutes during this first pediatric clinic hour of a new school year, I have planned at the suggestion of two staff members but with hesitation and humility, to speak to you not about children either well or sick, but about ourselves as responsible members, *all,* of a medical institution of learning in this day of cynicism and rebellion, of bad manners and "what do I get out of it" questioning, of little faith and rare equanimity.

Medicine is one of the old recognized professions. That is, as Dean (Emeritus) Roscoe Pound says, "an organized calling in which men pursue a learned art and are united in the pursuit of it as a public service—no less a public service because they may make a livelihood thereby. Here, from the professional standpoint, there are three essential ideas—organization, learning and a spirit of public service. The gaining of a livelihood is not a professional consideration. Indeed, the professional spirit, the spirit of a public service, constantly curbs the urge of that instinct."[5]

As students in the clinical years you now join the hospital staff as physicians—without degrees and without licenses and without adequate experience, but physicians you are, nevertheless. As such you are members of a goodly company of persons directly responsible for the health of your fellow men and indirectly, but no less vitally, sharing responsibility for the health and the welfare of society. Leaders in our profession have viewed the far horizon and have envisioned us in the vanguard in the march of civilization. Writing many years ago, Virchow, father of cellular pathology, prophesied:

> Should medicine ever fulfil its great ends, it must enter into the larger political and social life of our time; it must indicate the barriers which obstruct the normal completion of the life-cycle and remove them. Should this ever come to pass, medicine, whatever it may then be, will become the common good of all. It will cease to be medicine and will be absorbed into that general simplified body of knowledge which is identifiable with power. . . . When we have exact knowledge of conditions of existence of individuals and of peoples, then only will it be possible for the laws of medicine and philosophy to gain the credence of general laws of humanity. Then only will the Baconian "Knowledge is Power" become accomplished fact.

And more recently, in our own day and generation and in our own school of medicine, Dr. Winternitz had the vision to fashion an Institute of Human Relations where medicine would take its vital and rightful place in a grouping together of biological and social sciences seeking, with law and religion, through physical, mental, and spiritual liaison to discover the bases upon which a better society might be builded and human welfare promoted. Medicine of the past sought to make possible a healthy body—Curative Medicine; in a confused way it now seeks a healthy mind in a healthy body—Mental Hygiene; but, now and in the future, it must seek integration with life—a healthy person in a healthy society.[3]

The physician has his roots deep in the soil of the past, for tradition to him "is not a barren pride in departed glories"—as a statesman once said in reference to British political tradition, "it is something from which he derives a profound assurance, a sense of destiny, and a determination never to abandon what has been purchased" with such labor, skill, devotion, and sacrifice "by those who have gone before him." Medical "tradition is not a recollection of the dead; it is real and living and growing. It rests upon an unspoken, and perhaps in many cases, unrealized faith in the undefeated continuity of the [profession]. A man with a deep sense of continuity sees himself not as an accidental unit doomed to vanish in a few years but as one of a great human procession, influenced and helped by those who have gone before him, responsible in his turn for giving help and encouragement to those who will come after."[4]

You are the inheritors of this tradition and the beneficiaries of many generous philanthropies and appropriations; the future of medicine will be as you plan and work. As already stated, you are physicians in fact if not in name and you have assumed responsibility for health and happiness (in part) of human individuals based on the scientific training and knowledge you have received here and elsewhere and guided by such wisdom as you possess and develop. You are members now of a noble profession—one enriched by the careful observations and correlations and patient investigations of thousands of your devoted and indefatigable professional ancestors whose contributions and example are your priceless heritage.

And thus, attention having been directed to some of our indebtednesses, I come to the central theme of my remarks; I shall put it in the form of a quotation from an address by the great psychologist and philosopher, William James. Said he:

> Does not the acceptance of a happy life upon such terms involve a point of honor? Are we not bound to take some suffering upon ourselves, to do some self denying service with our lives in return for all those lives upon which ours are built? To hear the question is to answer it in but one possible way, if one have a normally constituted heart.[3]

It is a cliché to say that great universities are builded not with bricks and mortar but with great teachers. For are we not all teachers, practitioners, and students!—in varying degrees, of course, but none-the-less each of us here functions in all of these categories. Do not think for a moment because academic protocol designates you as "students" or "clinical clerks" and some of us as "faculty" that the sick, distraught human beings whom you will see as patients are going to make or should make any such distinction. And do not think or thoughtlessly assume that the reputation and the achievements and the prestige of the Yale University School of Medicine rest alone upon faculty, laboratories, or hospital; upon *your* qualities of character, mind, and heart also rest challenging responsibilities and great privileges, upon your sense of oneness in great endeavor, upon your loyalties and devotion to duties, opportunities, and team work, upon conduct, humanitarian and moral, as well as interests, intellectual and scientific —upon these equally rests the fair name of our School. Greatness in a school of medicine, I say, with all the strength of firm conviction and all the earnestness of worthy ambition for this institution, derives from *all* of the constituent members just as truly as it derives from human beings rather than from buildings and equipment.

To be a physician—that is a great responsibility, yes, but is it not a great privilege also? Think of your kinship with the great men and women who have wrought brilliantly and effectively in the advances of medical science; think of those patient scholars equally gifted and equally worthy but unacclaimed because their results, as we say, were "negative"; think of the thousands of devoted, industrious, competent practitioners of the science and art of medicine; think of the teachers, public health workers, administrators; think of the rich opportunities to deal with people and families in all the vagaries and vicissitudes, in the successes and failures of life; think of the sickness of society and of the opportunities to do something to bring understanding, healing, and correction; and just think very seriously of the fact that you are here where many others long to be—others, perhaps, more, or at least equally, deserving of the privilege and who will never gain admission to any school of medicine! Think on these things, I beg you, and realize and act upon the fact that you are privileged far beyond the vast number of your fellow men.

In these so-called "clinical years," what are the senior students, *i.e.,* the faculty, endeavoring to do for you the junior students? In pediatrics, are we going to try to "cover the ground," as some would suggest, or give a "comprehensive course"? Are we going to discuss the natural history and treatment and family and community repercussions of every important disease which may afflict the child? Are we going to point out each milestone on the pathway of growth and development of the growing organism and the maturing personality? No, what you acquire in the way of facts is largely incidental and can be gotten perhaps more easily from books and scientific journals without the aid of expensive hospitals, laboratories, and preceptors. What we in pediatrics seek to do by example, word, and deed is to demonstrate a way of life, a way of medical life, more narrowly—a way of pediatric life. How we obtain vital data in the child's history and appraise his environment, learn about family life, mother and father, sisters and brothers; what has taken place in his maturation; what illnesses he has had, what preventive measures have been taken, what indicated; what behavior reactions does he have; what signs and symptoms of illness does he exhibit; what diagnostic procedures are indicated; what treatment is necessary for the patient in the bed (and the sick parents in the waiting room); what report is to be made to the physician who referred the patient (not the "L.M.D.," please) or the visiting nurse who brought him in; what can be done in the home to create a happy and healthful environment; how can the nurse and medical social worker be helpful; what public health contacts are indicated? These are but sample questions and problems which are to be dealt with in a pediatric way of life and require an integration not to be secured from books and lectures and not easily measured by examination marks.

You have had opportunities and facilities for acquiring knowledge and methodologies in the basic medical sciences. By using this intellectual equipment, by observing and emulating the professional procedures of your more experienced fellow students (the clinical faculty), by examining and by careful, kindly questioning of patients or parents, by studying the literature, by discussing data with student and faculty colleagues—thus will you acquire skills in the practice of medicine and learn how to think about clinical problems, how to approach various situations and deal effectively and wisely with them. The internship is the crown and glory of this experience and that is the reason it matters so little, relatively speaking, whether your hospital service be "straight" or "rotating," surgical or pediatric; what

greatly matters is fine quality and high standards and fair critiques of performance and conduct, professional and personal.

I might add, by way of footnote, that although we make no systematic effort to give a comprehensive "quiz course" in pediatrics, you will become familiar with the important aspects of the subject if you attend faithfully all the "required" courses in pediatrics given during the two clinical years; courses which vary in form and substance and which you well know you are not required, except by honor and self-interest, to attend.

By emulation, by repetition, by steady application, by experience and by practice, will you become what you all, I hope, seek to become—great physicians? Something more, I think, is required—something at the heart of all great achievement. What you call that "something more" matters not—character, wisdom, inner security—not the kind furnished by government subsidies or by private annuities but by your faith, faith in something, faith which is your own and gives meaning to life, a something of incorruptible good which in our sickworld society is badly needed. The poets know of what I am speaking:

> Wisdom was never learned at any knees,
> Not even a father's, and that father a king.
> . . . . . I am not one
> Who must have everything, yet I must have
> My dreams if I must live, for they are mine.
> Wisdom is not one word and then another,
> Till words are like dry leaves under a tree;
> Wisdom is like a dawn that comes up slowly
> Out of an unknown ocean.[6]

And thus with training and wisdom may you attain to that group envisioned by Thomas Hardy:

> We would establish those of kindlier build,
> In fair compassions skilled,
> Men of deep art in life development.[2]

References

1 Halliday, James L.: *Psychosocial medicine—A study of the sick society.* New York, W. W. Norton and Company, Inc., 1948, p. 209.

2 Hardy, Thomas: *The dynasts—an epic drama.* London, Macmillan and Company, Ltd., 1921. "Chorus of the Pities," p. 3.

3 James, William: *The will to believe.* New York, Longmans Green and Company, 1907. "Is life worth living," p. 50.

4 Menzies, Robert Gordon: It is a good tradition—it cannot die. The New York Times Magazine, July 10, 1949.

5 Pound, Roscoe: The professions in the society of today. N. England J. M., 1949, *241*, 351.

6 Robinson, Edwin Arlington: *Collected poems.* New York, The Macmillan Company, 1946. "Tristram," p. 726.

THE ROLE OF CERTAIN STEROIDS IN THE ADRENAL-HYALURONIDASE RELATIONSHIP*

JEANETTE C. OPSAHL

It has been reported previously that the dermal spread of India ink with hyaluronidase is markedly influenced by the hormones of the adrenal cortex.[5,6] Removal of the adrenals resulted in an enhancement of the spreading reaction, while the administration of a potent extract of the adrenal cortex either in the adrenalectomized or normal animal inhibited spreading. However, desoxycorticosterone acetate was found to be without effect.

These observations indicated some specific relationship between hyaluronidase inhibition and chemical structure of the adrenal cortex steroids. In the present study several pure steroids have been investigated in an attempt to define more accurately the structural or hormonal factors that are related to the inhibition of the hyaluronidase-enhanced spreading phenomenon.

The primary object of this study was to determine which steroids would cause an inhibition of the spreading reaction when conditions were provided that permit adrenal cortical extracts to exert maximal effects. It was hoped that a better understanding of the adrenal-hyaluronidase relationship would be obtained in this way, although it was recognized that conditions of the experiments should be altered in order to obtain complete information regarding the influence of steroids on the spreading reaction.

Materials and methods

The general methods and precautions have been described in some detail.[5,6] CBA mice, 10 to 12 weeks old and with equal distribution of sex, were used in all experiments, with the exception of the local intradermal injection studies. The volume of the steroid solution injected was either 0.5 or 1.0 cc. except in the local injections. In the latter a total volume of 0.5 cc. was employed and this volume included steroid and India ink either with or without hyaluronidase. The hyaluronidase preparation used in the majority of the studies was the standardized preparation W-108-A and was supplied by Dr. Joseph Seifter of the Wyeth Institute.

In the mouse experiments, bilateral intradermal injections of India ink were made. During the early observations a saline control injection was made on one side and hyaluronidase mixture was injected on the other side. However, it became evident that none of the steroids caused definite responses in the non-enzyme control area.

*From the Department of Bacteriology and Immunology, Yale University School of Medicine.

Received for publication November 1, 1949.

Therefore, in the majority of experiments presented here, enzyme was used in both injections, thus doubling the number of observations for a given substance.

The steroids were dissolved in sesame oil, dissolved in absolute ethanol and then diluted with water to make a suspension in 10% alcohol, or a suspension was made by thorough grinding and diluting with 0.9% sodium chloride solution. The alcohol-water suspensions were very poor, but the plain saline suspensions appeared fine and well dispersed, although the steroids settled out rapidly since no suspending agent was used.

Lipo-Adrenal Extract (Upjohn) and adrenal cortical extract (Wilson) were used as positive controls, for both of these preparations had been shown in previous experiments to inhibit the spreading reaction. The method of handling these preparations has been described in detail in earlier publications.

The general plan of the experiments was to inject the steroid into normal mice. After an interval of from one to six hours, bilateral intradermal injections of India ink and hyaluronidase in a total volume of 0.05 cc. were made. One hour later the mice were killed by fracturing the spinal cord at the cervical level; the skins were then removed. The area of spreading was measured as described in previous reports.

Experimental

The results obtained with six steroids together with control studies with Lipo-Adrenal Extract and adrenal cortical extract are presented in Tables 1 and 2. Interpretation of activity in the spreading phenomenon is made from the last column which shows the percentage change in the hyaluronidase-enhanced area of spread that has resulted from the administration of the substance under investigation. It will be seen that Compound E given intraperitoneally, intramuscularly, subcutaneously, or locally caused a marked and consistent inhibition of the spreading reaction. The inhibition of spread by Compound E when given locally at the site of hyaluronidase and India ink injection has been confirmed in several preliminary experiments with mice. The local effects produced by the other steroids when tested in mice were equivocal and, therefore, have not been included here.

Compound A inhibited spreading when administered systemically, but no effect was noted on local injection. The results with Compound A were not so definite as those with Compound E, but since a consistent inhibition was noted, there can be no doubt that this steroid was qualitatively similar to Compound E.

In the four experiments with testosterone, no effect on spreading was noted. An analysis of results in males and females separately revealed no differences between the sexes. It has been observed consistently that there is no sex difference in the spreading phenomenon and this finding was reported in an earlier publication.[5]

TABLE 1

THE INFLUENCE OF CERTAIN STEROIDS ON THE DERMAL SPREADING OF INDIA INK WITH HYALURONIDASE: I. ADRENAL CORTICAL HORMONES.

Experimental animal	*Route of administration*	*Dose*	*Type of diluent*	*Time of steroid injection*	*Area of spreading with hyaluronidase and India ink*		
					Control injected with diluent†	*Experimental injected with steroid†*	*% Change from control*
		mg.		*hours*	*sq. mm.*	*sq. mm.*	
		COMPOUND E (11-dehydro, 17-hydroxycorticosterone)					
Mouse	i.p.	1.0	saline	1	374 (12)	223 (6)	—40
"	i.p.	1.0	saline	3	374 (12)	164 (10)	—56
"	i.m.	1.0	saline	3	366 (12)	248 (12)	—32
"	s.c.	1.0	oil	3	310 (6)	223 (8)	—28
Rabbit	local	0.5	saline	0	3000 (2)	2000 (2)	—33
		COMPOUND A (11-dehydrocorticosterone)					
Mouse	i.p.	5.0	saline	3	380 (8)	254 (4)	—33
"	i.p.	1.0	10% ETOH	3	351 (8)	197 (8)	—44
"	i.p.	0.5	10% ETOH	3	374 (6)	339 (4)	— 8
"	i.m.	5.0	saline	3	346 (8)	310 (4)	—10
"	s.c.	1.0	oil	1	261 (4)*	220 (4)*	—16
"	s.c.	0.5	oil	1	185 (2)*	155 (2)*	—16
"	s.c.	0.5	oil	3	180 (4)*	173 (4)*	— 4
"	s.c.	0.5	oil	3	235 (4)*	222 (4)*	— 6
Rabbit	local	0.5	saline	0	2800 (1)	3100 (1)	+11
		LIPO-ADRENAL EXTRACT (UPJOHN)					
Mouse	s.c.	0.25 cc.	oil	1	375 (4)	239 (4)	—36
"	s.c.	0.25 cc.	oil	24	331 (4)	287 (4)	—13
		ADRENAL CORTICAL EXTRACT (WILSON'S)					
Mouse	i.m.	0.5 cc.	saline	3	346 (8)	271 (6)	—22

* Lower potency hyaluronidase than employed in the other studies here reported.

† Numbers in parentheses represent the number of animals employed. Since each animal was bilaterally injected with the hyaluronidase-India ink mixture, the actual number of observations is double the number of animals.

TABLE 2

THE INFLUENCE OF CERTAIN STEROIDS ON THE DERMAL SPREADING OF INDIA INK WITH HYALURONIDASE: II. RELATED STEROIDS.

Experimental animal	*Route of administration*	*Dose*	*Type of diluent*	*Time of steroid injection*	*Area of spreading with hyaluronidase and India ink*		
					Control injected with diluent†	*Experimental injected with steroid†*	*% Change from control*
		mg.		*hours*	*sq. mm.*	*sq. mm.*	
	TESTOSTERONE						
Mouse	i.p.	5.0	saline	3	380 (8)	403 (7)	+ 6
"	i.p.	1.0	saline	3	374 (12)	370 (4)	— 1
"	i.m.	1.0	saline	3	366 (12)	386 (19)	+ 5
Rabbit	local	0.5	saline	0	1800 (1)	1800 (1)	0
	ESTRADIOL BENZOATE						
Mouse	i.p.	5.0	saline	3	380 (8)	379 (8)	0
"	i.p.	1.0	saline	3	374 (12)	359 (4)	— 4
"	i.m.	1.0	saline	3	366 (12)	304 (13)	—17
Rabbit	local	0.5	saline	0	1500 (1)	1500 (1)	0
	PROGESTERONE						
Mouse	i.p.	5.0	saline	3	380 (8)	362 (8)	— 3
"	i.p.	1.0	saline	3	374 (12)	387 (4)	+ 3
"	i.m.	1.0	saline	3	366 (12)	306 (10)	—16
"	i.m.	1.0	oil	3	309 (8)	296 (10)	— 4
Rabbit	local	0.5	saline	0	1250 (2)	1650 (2)	+28
	PREGNENOLONE						
Mouse	i.p.	5.0	saline	3	380 (8)	398 (8)	+ 5
"	i.p.	1.0	saline	3	374 (12)	388 (4)	+ 4
"	i.m.	5.0	saline	1	330 (4)	334 (5)	+ 1
"	i.m.	5.0	saline	3	330 (4)	275 (6)	—16
"	i.m.	5.0	saline	6	330 (4)	330 (6)	0
"	i.m.	1.0	saline	3	366 (12)	317 (6)	—13
Rabbit	local	0.5	saline	0	2300 (1)	2650 (1)	+15

† Numbers in parentheses represent the number of animals employed. Since each animal was bilaterally injected with the hyaluronidase-India ink mixture, the actual number of observations is double the number of animals.

Estradiol benzoate, progesterone, and pregnenolone gave equivocal results, but it appears justifiable to conclude that under the experimental conditions employed, these steroids did not affect definitely the spreading reaction.

In agreement with earlier studies, a definite inhibition was obtained with the two adrenal extracts. It is interesting to note that there appears to be some decrease in activity in the 24 hours following the subcutaneous administration of the Lipo-Adrenal Extract.

Discussion

The results presented here, together with the earlier observation of a lack of inhibition by desoxycorticosterone, are very suggestive of a correlation between the C-11 oxygenated adrenal steroids and inhibitory activity in the hyaluronidase-enhanced spreading phenomenon. Of seven steroids that have been studied only two have definitely shown activity. Furthermore, these compounds, E and A, are the only ones in this series that have the carbohydrate metabolism characteristics of the C-11 oxygenated adrenal steroids. Additional evidence in support of this correlation is the observation that A is less active than E. Although quantitative interpretation cannot be drawn from these studies, the difference in activity between compounds E and A appears to be rather definite. A similar difference in the carbohydrate metabolism influence of these two steroids is well established.

The experiments described here were designed so as to obtain comparable data with the different steroids. In order to accomplish this, it was necessary to test all compounds under identical conditions. For example, there was some indication that the adrenal cortical extracts exerted their maximal influence on the spreading reaction within a period of from one to six hours following administration of the extract. Since it was the primary objective of this investigation to study compounds that might exhibit the adrenal cortical effect, the steroids were all administered within this time interval prior to the injection of the hyaluronidase-India ink mixture.

The lack of activity observed for testosterone, estradiol benzoate, progesterone, and pregnenolone must be interpreted cautiously. The dosages employed for the hormonally active steroids were large enough to give the conventional end-organ responses. Actually the dosage of estradiol benzoate and of progesterone was much larger than is required for maximal hormonal responses. However, the time of action was far too short for these hormonal effects fully to be manifested. In dealing with these sex hormones, days rather than hours are required for complete anatomical responses to the

hormones. On the other hand, adrenal effects such as glycogen storage are obtained within a matter of hours following administration of the hormone. It is possible that different results would have been obtained with the sex hormones if a longer time-interval had been used. However, this variation in conditions was outside the scope of this study. In the case of the adrenal steroids, the time relationship was compatible with that required for a primary hormonal response.

Other investigators have observed an inhibition of the spreading reaction by estrogens. For example, Sprunt[7,8] found that both estrone and estradiol-dipropionate inhibited India ink spreading in normal and in castrate rabbits when rather large doses were administered daily over long periods of time. Lurie and Zappasodi[3] have found that as compared with female rabbits, the males showed a decreased spread of India ink. As noted above, this observation has not been substantiated for mice.

Contrary to the effects with estrogens, Lurie and Zappasodi[4] found that progesterone increased the area of India ink spreading in the rabbit. Because of the difference in the time factor, neither the estrogen nor the progesterone studies of these investigators can be compared directly with the experiments presented here.

Regardless of the obvious importance of varying the time interval for the different steroids, the conclusion is justified that under conditions necessary for the C-11 oxygenated adrenal steroids to exert a pronounced inhibition of hyaluronidase-enhanced spread of India ink, testosterone, estradiol benzoate, progesterone, and pregnenolone appear to be inactive.

The recent observations that Compound E and the pituitary adrenocorticotrophic hormone (ACTH) are active agents for the treatment of rheumatoid arthritis and possibly for other diseases that are relieved by pregnancy[1,2] have made it essential to develop laboratory assay procedures that can be used to study the fundamental biochemical properties of this field of chemotherapy. As it is possible that hyaluronic acid metabolism is involved in the manifestation of certain of the arthritides, it is logical to examine the hyaluronidase inhibiting activity of compounds that influence the clinical condition in rheumatoid arthritis. At the present time this comparison is impossible since completely documented results of clinical investigations are very meager. Nevertheless, the general technique employed in the present study should be extended so that correlations can be made when clinical results become available. In establishing this correlation, the time factor emphasized in the preceding discussion should be given due consideration, for it is possible that steroids having beneficial clinical effects

will exhibit these effects after varying time intervals. One of the remarkable features of the Compound E treatment of rheumatoid arthritis is the rapidity of action. This characteristic is apparent not only in certain primary hormonal responses such as glycogen storage, but also in its inhibition of hyaluronidase-enhanced spreading.

Conclusions

1. Compound E and, to a lesser extent, Compound A inhibit the spreading of intradermally injected India ink with hyaluronidase.

2. Testosterone, estradiol benzoate, progesterone, and pregnenolone, when tested under conditions necessary for the optimal inhibitory activity of adrenal cortical extracts, did not have a definite influence on the spreading phenomenon.

3. The evidence suggests that inhibition of the spreading reaction by the adrenal hormones is restricted to steroids that have an oxygen at Carbon-11.

References

1 Hench, P. S.: Proc. Mayo Clin., 1949, *24*, 167.
2 Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F.: Proc. Mayo Clin., 1949, *24*, 181.
3 Lurie, M. B. and Zappasodi, P.: Proc. Soc. Exp. Biol., N. Y., 1939, *42*, 741.
4 Lurie, M. B. and Zappasodi, P.: Arch. Path., Chic., 1942, *34*, 151.
5 Opsahl, J. C.: Yale J. Biol., 1949, *21*, 255.
6 Opsahl, J. C.: Yale J. Biol., 1949, *21*, 487.
7 Sprunt, D. H. and McDearman, S.: Endocrinology, 1940, *27*, 893.
8 Sprunt, D. H., McDearman, S., and Raper, J.: J. Exp. M., 1938, *67*, 159.

THE RISE OF SCIENTIFIC ACTIVITY IN COLONIAL NEW ENGLAND*

FREDERICK G. KILGOUR

Scientific tradition in New England had its beginnings in and around Boston shortly after the year 1712. The main purpose of the present paper is to describe this early stirring of scientific activity, and to present some of the factors that may have influenced it. It is true that this scientific activity was elementary compared with the contemporaneous European science. Nevertheless, early eighteenth-century New Englanders made two important contributions, one of which was the first report on record of the hybridization of plants, and the other, the first extensive use in the western world of inoculation for smallpox.

Among the Puritans who came to New England in the 1630's, were a few men who were interested in science. But their interest was never sufficiently vigorous to give science any real place in Puritan culture, and it gradually ran down like a clock, reaching its slowest point at the turn of the century. Then, suddenly, there was a new burst of activity which developed rapidly and became one of the main roots of American scientific tradition.

During the seventeenth century the most prominent scientist in the British colonies was John Winthrop, Jr. (1606-1676), the eldest son of the first governor of the Massachusetts Bay Colony. Winthrop came to Boston in 1631, bringing with him his library of over a thousand volumes to which he subsequently made many additions. Two hundred and seventy volumes from Winthrop's library are housed in the Society Library of New York City. These 270 volumes are the largest segment of a seventeenth-century colonial library in existence today. An analysis of their titles reveals that there are more books on chemistry than on any other scientific subject.[1]

The predominance of chemical books in Winthrop's library is not surprising, since most of Winthrop's scientific activity was related to chemistry. He believed that the future of New England lay in manufacture and commerce, not in agriculture; history proves him to have been foresighted.

---

* Presented before the Beaumont Club on October 21, 1949.

[1] Browne, C. A.: Scientific notes from the books and letters of John Winthrop, Jr., *Isis*, 1928, *11*, p. 326.

Having a practical interest in the development of industry, he attempted to organize a salt works on Fisher's Island as early as 1640. Like many of his manufacturing projects, the salt works was doomed to financial failure. About 1644 he set up iron furnaces at Lynn and Braintree, Massachusetts, but after a short success his iron works were also forced to close down. Undaunted by these failures, Winthrop continued his industrial ventures after he moved to Connecticut in 1647. He started a second iron works at New Haven and opened a graphite mine, but neither was a financial success.

Winthrop also applied his knowledge of chemistry in the practice of physick. His attractive personality and his readiness to take care of anyone from a colonial governor to a sick Indian made him one of the most beloved men in the colony. Cotton Mather wrote ". . . that where-ever he came, still the Diseased flocked about him, as if the Healing Angel of Bethesda had appeared in the place . . ."[2] His remedies were mostly the simples of the Galenists, but he may also have prescribed some of the astounding seventeenth-century concoctions. On January 26, 1656, Sir Kenelm Digby sent him several prescriptions including one for ". . . miraculous cures in all sortes of vlcers, and in knitting soddainly broken bones. . . . Beate to subtile pouder one ounce of crabbes eyes [in Latin, called Oculi cancrorum], then putt vpon it in a high glasse (because of the ebullition) foure ounces of strong wine-vinegar. It will instantly boyle vp extremly; lett it stand till all be quiett; then straine it through a fine linon; and of this liquor (wch will taste like dead beere; without any sharpness) giue two spoonefuls att a time to drinke, three times a day: and you shall see a strange effect in a weeke or two."[3] Winthrop may have prescribed this horror, but one hopes, with Oliver Wendell Holmes, that he did not. Another of Winthrop's remedies, *rubila,* was apparently a product of his own invention said to consist of antimony sulphide, nitre, and a little salt of tin, with something added to make the powder red.[4] *Rubila,* whose formula was kept secret, was supposed to cure all manner of diseases, and was undoubtedly America's first patent medicine. Its popularity was tremendous and it was even exported to England where it was in considerable demand.

When the Royal Society was being formed in 1662, Winthrop was in England and was asked to become a charter Fellow, which honor he readily

---

[2] Mather, Cotton: *Magnalia Christi Americana,* London, Printed for Thomas Parkhurst, 1702, bk. II, p. 31.

[3] *Coll. Mass. Hist. Soc.,* 3d ser., 1849, *10, p.* 17.

[4] Holmes, O. W.: *Medical essays,* 1842-1882. Boston, Houghton, Mifflin and Co., 1888, p. 335, and Browne, *op. cit.,* p. 336.

accepted. Returning in 1663 to Connecticut, being then Governor of that colony, he brought with him a little astronomical telescope about three and a half feet long. He reported in 1664 that through it he had seen a body that he thought to be the fifth satellite of Jupiter, and he requested that his friend Sir Robert Moray, President of the Royal Society, attempt to obtain a confirmation of his observation. It was not until 1892 that a fifth Jovian satellite was discovered, and it is certain that Winthrop confused a fixed star with Jupiter's family of satellites.[5]

Winthrop presented his little telescope to Harvard College in 1672, and Thomas Brattle (1658-1713) used it to observe the famous comet of 1680. Brattle sent his observations on the comet to John Flamsteed, the first Astronomer Royal, at Greenwich. Flamsteed in turn sent Brattle's observations to Isaac Newton, who used them in his great *Principia*[6] to prove that comets traveled in paths that were determined by the law of gravity, which he was presenting to the world for the first time. Newton praised "the observer in New England," together with some European astronomers who, like Brattle, had determined the path of the comet with reference to the fixed stars instead of using the system of co-ordinates known as altitudes and azimuths. The latter method of fixing the location of astronomical bodies yields different results for different places of observation, and it was difficult for Newton to obtain satisfactory results by reducing the altitude and azimuth locations to points on the celestial sphere.

Brattle continued his scientific work, but accomplished little of real significance. In 1694 and 1703 he observed solar eclipses and in 1700 and 1703 he observed lunar eclipses.[7] In 1707 he observed another lunar eclipse.[8] The low state of science in New England in the first decade of the eighteenth century is perhaps best pictured in Brattle's own words in a letter written to Flamsteed on December 15, 1703:

> Sr, by what I have don you may give some guess at my inclinations, how I spend ye greatest part of my time, & what I would do if I had better conveniences, helps & encouragements, for to tell ye truth, I am here all alone by myself, without a meet help in my Studies as well as in ye more common sense & that little insight wch I have into these matters, I have gotten it, as they say, proprio Marte, there never having

[5] Streeter, J. W.: John Winthrop, Junior, and the fifth satellite of Jupiter. *Isis*, 1948, *39*, pp. 159-63.

[6] Book III, prop. xli, prob. xxl.

[7] Brattle, Thomas: An account of some eclipses of the sun and moon. *Philos. Tr. R. Soc. London*, 1704-05, *24*, pp. 1603-08.

[8] Brattle, Thomas: Observatio eclipsis lunaris peracta Bostonij Nov. Anglorum, die quinto Aprilis vespere, A.D. 1707. *Philos. Tr. R. Soc. London*, 1706-07, *25*, pp. 2471-72.

ben any one person that could give me y^e^ least Instruction, Assistance or Satisfaction in these Studies.[9]

Still further evidence of the small amount of scientific activity toward the end of the seventeenth century and in the first decade of the eighteenth is in a letter that Brattle sent to Flamsteed in 1705.[10] Brattle makes it perfectly clear that he was the only man in the Boston area who was engaged in science; at the turn of the century he was probably New England's only scientist.

For I Know of no body here but myself that applies himself to this Kind of Study & I never pretended to more than to be a Lover of them, or a Friend & Wellwisher to them. Nor can any considerable Attainments, much less Improvem^ts^ be rationally expected from one that has laboured all along under such mighty disadvantages, for, as I hinted in my last, I never had any body to direct me, to assist me, or encourage me, but have ben forced to pick my way, & to get over y^e^ rubbs w^ch^ lay in it as well as I could myself. All that I have don has ben purely Accidentall, & now a step & then a step, in so much that I have very often bewail'd my misfortune that I should spend so much time to so little purpose, being well assured I might have got & don more in 4 or 5 years, had I had all necessary Conveniences & Assistancees, than under my unhappy circumstances I have ben able to do in 4 or 5 & Twenty.

Shall I trouble you w^th^ one instance instead of many? Sonn after I began to look into these things, I perceiv'd that nothing w^s^ to be don without Euclid. I had Barlow then by me, and with once reading I understood his 4 first propositions, but Stopt at y^e^ 5^th^, & was discouraged from taking any pains to understand it, for I imagin'd if I should get over that, yet w^t^ follow'd would be Still harder & harder. However, I could not forbear looking into other Authors, & at length li't upon Schottus, w^o^ at y^e^ end of y^e^ 4^th^ proposition has these words:—*Sequens propositio est pons Asinom, quem qui transierit Securus in reliquis perget.* Thought I hereupon, is it so? I will try presently, & found his words true, for I immediately got over that difficulty, & soon after went through his first 6 books & his 11^th^ & 12^th^, but without that luckly hint, I might possibly not have so much as understood Euclid to y^e^ day. How happy are those, have I thought with myself many times, w^o^ set out Early, & have a guide to direct them, so that they never go a Step out of the way, nor make any Stop in the way. . . .

But the situation that Brattle lamented was not to continue for long. Less than ten years later that eminent Puritan divine, Cotton Mather (1663-1728), sent to the Royal Society thirteen letters dealing with various natural phenomena. Seven of these letters went to Dr. John Woodward and the other six to Richard Waller. Woodward had previously requested Mather

---

[9] I am deeply indebted to Mr. John W. Streeter of the Department of Astronomy at Vassar College for furnishing me this reference and the following. The quotations are from typescripts in Mr. Streeter's possession of the original Brattle letters in Flamsteed MSS, volume 41 at the Royal Observatory. Thomas Brattle to Flamsteed dated "Boston in New England, 15 Decem^b^ 1703."

[10] Thomas Brattle to Flamsteed. "Boston in New England Feb. y^e^ 8^th^ 1704/5."

to send him ". . . such subterraneous curiosities, as may have been in these parts of America mett withal."[11] Mather called the letters *Curiosa Americana,* and from 1712 to 1724 he sent in all eighty-two letters to the Royal Society.[12] The first group treated many subjects: giants, birds, plants, imagination, monstrous births, dreams, etc. Very few of the observations had actually been made by Mather, and some of them were at least thirty years old.

The second group (ten letters in 1714) dealt with contemporary observations made by his "neighbours." The next year, instead of sending his *Curiosa Americana,* Mather sent the manuscript of a book entitled "The Christian Virtuoso." When the book was published in 1720—the title-page reads 1721—it was given the title *The Christian Philosopher: A Collection of the Best Discoveries in Nature with Religious Improvements* (London, Printed for Eman. Matthews, 1721). The author explained the purpose of his book in the first sentence of the introduction: "The essays now before us will demonstrate, that *Philosophy* [science] is no *Enemy,* but a mighty and wondrous *Incentive* to *Religion*"; and some of the typical chapter headings of *The Christian Philosopher* are "Of the Fixed Stars, Of Comets, Of the Snow, Of Minerals," and the last and most extensive, "Of Man." Mather drew his scientific knowledge from many up-to-date sources, and he particularly acknowledged his indebtedness to "the Industrious Mr. RAY, and the Inquisitive Mr. DERHAM." It was the former's *Wisdom of God Manifested in the Creation* and the latter's *Astro-Theology* from which Mather had drawn extensively. Despite the theological tenor of these two titles, they were excellent scientific books. William Derham and John Keill, another author from whom Mather borrowed, were thorough-going Newtonians, and they so firmly convinced Mather of the validity of Newton's theories that Mather wrote of ". . . the admirable Sir *Isaac Newton,* whom we now venture to call the *Perpetual Dictator* of the learned World, in the *Principles of Natural Philosophy.*"[13] Each chapter of *The Christian Philosopher* is divided into two parts; the first section sets forth the scientific knowledge on the subject under discussion, and the second gives the "Religious Improvements," wherein Mather shows the great wisdom and glory of God as revealed in Nature.

Mather's book contains only a few original observations, but at the

[11] Kittredge, G. L.: Cotton Mather's election into the Royal Society. *Publ. Colonial Soc. Mass.,* 1912, *14,* p. 83.
[12] Holmes, T. J.: *Cotton Mather; a bibliography of his works.* Cambridge, Harvard University Press, 1940, 3 vols., I, pp. 199-207.
[13] Mather, Cotton: *Christian philosopher,* p. 56.

time the manuscript was prepared in 1715 it contained the earliest known account of plant hybridization. On pages 124 and 125 of *The Christian Philosopher* we find the following:

> That I may a little contribute my *two Mites* to the illustration of the way wherein *Vegetation* is carried on, I will here communicate a couple of Experiments lately made in my Neighbourhood.
>
> My Neighbour planted a Row of Hills in his Field with our *Indian corn*, but such a Grain as was colour'd *red* and *blue*; the rest of the Field he planted with Corn of the most usual Colour, which is *yellow*. To the most *Windward-side* this Row infected *four* of the next neighbouring Rows, and part of the fifth, and some of the sixth, to render them colour'd like what grew on itself. But on the *Leeward-side* no less than seven or eight Rows were so colour'd, and some smaller impressions were made on those that were yet further distant.
>
> The same Neighbour having his Garden often robb'd of the *Squashes* growing in it, planted some *Gourds* among them, which are to appearance very like them, and which he distinguish'd by certain marks, that he might not be himself imposed upon; by this means the Thieves 'tis true found a very *bitter Sauce*, but then all the *Squashes* were so infected and embitter'd, that he was not himself able to eat what the Thieves had left of them.

In the first case, that of the cross-fertilization of corn, Mather described the effect of xenia in producing the kernels of different colors on the infected ears and implied that the substance causing this discoloration is carried through the air by the wind. In the case of the squashes, there is some doubt as to whether the phenomenon that Mather described was due to metaxenia or to inheritance; the squash seed was probably impure.

The Indians had known of the hybridization of corn long before the English arrived, and it was their custom to plant their ceremonial corn in some secluded spot where it would not become infected by other corn. From a paper published in 1724 in the *Philosophical Transactions* of the Royal Society by Paul Dudley (1675-1751),[14] another New Englander, we learn that the Indians thought that the infecting substance was transferred through the roots of the corn. Dudley observed that the roots of corn never extended more than five feet from the base of the plant. He then gives several cases of cross-fertilization to show that the communication of color from one plant to another cannot take place through the roots. In so doing, Dudley also reveals how interested New Englanders were in this problem of hybridization.

The Reverend Mr. Mayhew, of Martha's Vineyard, had told Dudley of two cases of cross-fertilization that disproved the root theory. In one case

---

[14] Dudley, Paul: Observations on some of the plants in New England, with remarkable instances of the nature and power of vegetation. *Philos. Tr. R. Soc. London*, 1724, *33*, pp. 194-200.

Mayhew observed that blue corn had communicated its color to yellow corn over a distance of four or five rods, a distance greatly in excess of the possible length of ten feet of roots extending from two corn plants. Mayhew's other observation was of a case of cross-fertilization that had taken place across a broad ditch of water. After having stated that he was " . . . humbly of Opinion, that the *Stamina,* or Principles of this wonderful Copulation, or mixing of Colours, are carried thro' the Air by the Wind; and that the Time, or Season of it, is, when the Corn is in the Earing. . . ." Dudley also related an observation of one of his neighbours ". . . that a close, high board Fence, between two Fields of Corn that were of a different Colour, entirely prevented any Mixture or Alteration of Colour, from that they were planted with."[15]

Nehemiah Grew, an English botanist, in an address to the Royal Society in 1676, had suggested that plants reproduce sexually, and he elaborated this idea in subsequent publications. Cotton Mather not only knew of Grew's work, but he was also very familiar with the writings of John Ray, as has already been shown. Ray was sure that flowering plants reproduced sexually, and Mather had accepted this idea. And it is also clear from Dudley's phrase, "this wonderful copulation," that he too had accepted the theory of the sexuality of plants. At the time that Mather and Dudley were recording observations and experiments, several Englishmen were also working on the problem of cross-fertilization, but it was almost forty years later that J. G. Koelreuter did his classical experiments on hybridization.[16] Mather's reports on cross-fertilization were never incorporated into the literature of hybridization, but Dudley's work was used in Philip Miller's *Gardeners Dictionary,*[17] and through this medium had a wide circulation. These early investigations into the phenomenon of the cross-fertilization of plants were certainly as important as any other botanical research that was going on at the time.

Between 1716 and 1720 Cotton Mather sent twenty-seven letters to the Royal Society. Most of these *Curiosa Americana* were still observations made by Mather's "neighbours." One of the 1717 *Curiosa,* for instance, is the record of an eclipse observation made by Thomas Robie at Harvard. Of the eleven letters despatched in 1716, two are of great interest. In one

[15] *Ibid.,* p. 199.

[16] Koelreuter, J. G.: *Vorläufige Nachricht von einigen das Geschlecht der Pflanzen betreffenden Versuchen und Beobachtungen.* Leipzig, 1761-66.

[17] Miller, Philip: *The gardeners dictionary.* London, Printed for the Author, 1733. Article on "Generation." The first edition of Miller's *Dictionary* was published in 1724, the same year in which Dudley's paper appeared.

of them Mather described more completely the hybridization experiments included in his manuscript of *The Christian Philosopher,* and in the second he made some prophetic suggestions concerning smallpox inoculation.

Of all the eighty-two *Curiosa Americana* that Mather sent to the Royal Society, extracts of only the first group were ever published.[18] The article that directly followed the extracts of Mather's letters in No. 339 of the *Philosophical Transactions* was an account of smallpox inoculation that had been sent to the Royal Society by Emanuel Timonius in Constantinople.[19] Sometime before July 12, 1716, Mather had obtained a copy of this number of the *Philosophical Transactions,* presumably for the purpose of reading the extracts of his own letters. He also read Timonius' article, which impressed him with its suggestion for avoiding the ravages of the dread smallpox. Mather wrote to Dr. Woodward of the Royal Society on July 12, 1716, that he was ". . . in a favourable Opinion, of Dr. *Timonius's* cõmunication," and went on to tell how he had first learned of smallpox inoculation from his Negro servant, "many months before."

> Enquiring of my Negro-man *Onesimus,* who is a pretty Intelligent Fellow, Whether he ever had y^e^ *Small-Pox*; he answered, both, *Yes,* and, *No*; and then told me, that he had undergone an Operation, which had given him something of y^e^ *Small-Pox,* & would forever praeserve him from it; adding, That it was often used among y^e^ *Guramantese,* & whoever had y^e^ Courage to use it, was forever free from y^e^ fear of the Contagion. He described y^e^ Operation to me, and shew'd me in his Arm y^e^ Scar, which it had left upon him; and his Description of it, made it the same, that afterwards I found related unto you by your *Timonius.*
>
> This cannot but expire, in a Wonder, and in a request, unto my D^r^. *Woodward.* How does it come to pass, that no more is done to bring this operation, into experiment & into Fashion in *England?* When there are so many Thousands of People, that would give many Thousands of Pounds, to have y^e^ Danger and Horror of this frightful Disease well over with y^m^. I beseech you, syr, to move it, and save more Lives than Dr. *Sydenham.* For my own part, if I should live to see y^e^ *Small-Pox* again enter o^r^ City, I would immediately procure a Consult of o^r^ Physicians, to Introduce a Practice, which may be of so very happy a Tendency. But could we hear, that you have done it before us, how much would That embolden us![20]

Five years later, Mather had the opportunity to fulfill his resolve, for smallpox broke out in Boston in April 1721. Mather prepared a letter addressed to the physicians of Boston that he circulated in manuscript on

---

[18] Mather, Cotton: An extract of several letters from Cotton Mather, D. D. to John Woodward, M. D. and Richard Waller, Esq.; S. R. Secr. *Philos. Tr. R. Soc. London,* 1714-16, *29,* pp. 62-71.

[19] Timonius (Timoni), Emanuel: An account, or history, of the procuring the small pox by incision, or inoculation; as it has for some time been practised at Constantinople. *Philos. Tr. R. Soc. London,* 1714-16, *24,* pp. 72-82.

[20] Kittredge, G. L.: Some lost works of Cotton Mather. *Proc. Mass. Hist. Soc.,* 1911-12, *45,* p. 422.

June 6. The letter, most of which was subsequently printed in Boston newspapers, contained an abstract of Timonius' report and also an abstract of an account of smallpox inoculation by Jacobus Pylarinus of Venice that had appeared in the 1716 issue of the *Philosophical Transactions*.[21] Mather asked the physicians to consider this new and as yet untried method for the prevention of smallpox, and if they thought it wise to employ inoculation, he begged them to do so.

The method of inoculation then employed did not use an attenuated virus as do our present vaccines. The procedure was to scratch the arm of the person to be inoculated so as to draw blood. Then some pus from a pustule of a patient ill with smallpox was rubbed into the incision. The inoculate, as he was called, subsequently contracted smallpox, but the degree of his illness was supposed not to be as great as it would have been had he been accidently infected with the disease. There was really not much evidence to guarantee that inoculation would be successful if it were undertaken. Mather was not a physician and was unaware of the possible dangers. Dr. William Douglass, the only physician in Boston who had a medical degree (he having attended medical schools in Europe) was opposed to inoculation because it seemed to him that deliberately infecting people with smallpox could only result in more deaths. Douglass also reasoned that if more people were infected with smallpox, the dread disease would spread more widely.[22] Both of Douglass' objections were quite valid, in the light of contemporary knowledge, and he was able to turn all of the Boston physicians against inoculation, with the sole exception of Zabdiel Boylston.

Boylston had the courage to gamble with his little son's life. There was no point in inoculating himself, as he had already had smallpox, so on June 26, 1721, Boylston inoculated his six-year-old son, Thomas, and two of his Negro slaves aged thirty-six and two-and-a-half.[23] The inoculations were successful, but the people of Boston, who had for the most part sided with Douglass, were furious that the experiment should have been performed. And although Douglass had first objected to inoculation on creditable scientific grounds, the opposition between him and those who favored inoculation soon became a battle of personalities. The *Boston News-Letter* took up the fight in the favor of the opponents of inoculation, they being the

[21] Pylarinus (Pylarini), Jacobus: Nove & tuta variolas excitandi per tranplantationem methodus, nuper inventa & in usum tracta. *Philos. Tr. R. Soc. London*, 1714-16, *29*, pp. 393-99.

[22] Douglass, William: *Inoculation of the small pox as practised in Boston.* Boston, Printed and sold by J. Franklin, 1722, pp. 13-18.

[23] Boylston, Zabdiel: *An historical account of the smallpox inoculated in New England.* 2d ed., cor. Boston, Reprinted for S. Gerrish and T. Hancock, 1730, p. 2.

great majority of Bostonians. Boylston, however, had been encouraged by the success of his first three inoculations, and he had begun to inoculate others. At this, the fever of the opposition mounted. On August 24, 1721, Mather, who had been vigorous in his support of Boylston and inoculation, wrote in his diary, "The Town is become almost an Hell upon Earth." Even physical violence was attempted, and at about three o'clock on the morning of November 14th, someone threw a "fired Granado" into Cotton Mather's bedroom. It happened that Mather was not occupying the room at the time; he had taken into his house the minister from Roxbury for an inoculation, and it was he who was in the bedroom when the home-made bomb came in through the window. Fortunately the fuse came out of the bomb, so that it did not explode. Tied with a string to the fuse, so that the explosion of the bomb would not destroy it, was a little note. "COTTON MATHER. I was once one of your Meeting; But the cursed Lye you told of— —You know who; made me leave You, You Dog, and Damn You, I will Enoculate you with this, with a Pox to you."[24]

It was not until the early summer of 1722, when the epidemic had abated, that the opposition to inoculation began to subside. But by that time the value of the new procedure had been proved. The total number of inoculations that had been performed was 286, of which 281 "had a perfect Small-Pox by Inoculation."[25] Of the total number only six had died, and there is reason to believe that these six inoculates had been infected with smallpox before they were inoculated or died from other causes. The mortality of those inoculated was about 2.1 per cent, in contrast to the 14.9 per cent mortality of all those who had contracted the disease. Perhaps the value of the work done by the inoculators may be more fully appreciated by comparing the inoculation mortality of 2.1 per cent with the 8.5 per cent mortality of the total population.

After the furor over the smallpox inoculation died down Mather continued to send his *Curiosa Americana* to the Royal Society. From 1722 to 1724 he sent thirty-one letters, most of them containing reports on natural phenomena sent to him by his correspondents. Three of the ten letters that Mather despatched in 1724 serve as excellent examples to illustrate his habit of reporting events which had been reported to him. One letter contains an account of a high yield of "Salt of Tartar" resulting from the burn-

[24] *Boston News-Letter,* November 20, 1721. In his *Diary* Mather states that the note read, "COTTON MATHER, *You Dog, Damn you: I'l inoculate you with this, with a Pox to you.*" Mather, Cotton: *Diary,* Boston, Massachusetts Historical Society, 1912, 2 pt., II, pp. 657-58.

[25] Boylston, *op. cit.,* p. 34.

ing of a white oak tree that had been felled in Cambridge. Thomas Robie had already done a considerable amount of research on this problem, and his findings had been published in the *Philosophical Transactions* for 1720.[26] Two other letters deal with observations reported to Mather by the Reverend Christopher Toppan of Newbury. Mather described Toppan's report of "An Amphisbaena," a serpent with a head at each end and capable of motion in either direction, and the case of a man who had "lately Vomited a *Lizard*." Mather had not, as Whittier wrote in "The Double-Headed Snake of Newbury," gone

> ". . . galloping down
> All the way to Newbury town,
> With his eyes agog and his ears set wide,
> And his marvellous inkhorn at his side,"

but if he had, he would have found neither amphisbaena nor vomited lizard.

Paul Dudley also communicated descriptions of natural phenomena to the Royal Society, the most important being his paper describing the hybridization experiments already discussed. A paper dealing with the manufacture of maple sugar was his first to be published; it appeared in the April 1720 issue of the *Philosophical Transactions*. From Dudley's paper on maple sugar, whose medical virtues he claimed were higher than those of West Indian sugar, it is apparent that the technique for producing this confection has changed very little in the last two centuries. From 1720 to 1735 Dudley had twelve articles published in the *Philosophical Transactions*,[27] all of them dealing with subjects that can roughly be classified as natural history.

Thomas Robie (1689-1729) was the most significant and productive scientist in New England during the period from 1712 to 1724.[28] He was graduated from Harvard in 1708, and the year after he took his master's degree, in 1711, he was appointed the Harvard "Library-Keeper." The next year he became a tutor at Harvard, a position which he held until 1723. In 1712 Harvard had acquired an 8-foot telescope, and, using this instrument, Robie observed eclipses and immersions of Jupiter's satellites in 1713 and 1714. He continued to make observations of such astronomical

---

[26] Robie, Thomas: An account of a large quantity of alcalious salt produced by burning rotten wood. *Philos. Tr. R. Soc. London*, 1720-21, *31*, pp. 121-24.

[27] Shipton, C. K.: *Sibley's Harvard Graduates*. Cambridge, Harvard University Press, 1933, IV, p. 54.

[28] Kilgour, F. G.: Thomas Robie (1689-1729), colonial scientist and physician. *Isis*, 1939, *30*, pp. 473-90.

phenomena as solar and lunar eclipses, southings of the moon, the zodiacal light, and auroras during the next four or five years.

In 1719 Robie wrote a pamphlet that was probably the first scientific work by an American to be published in America.[29] There had been an amazing aurora on the night of December 11, 1719, and Robie's pamphlet is a description and explanation of it. Being a true man of science, Robie refused to interpret the dreadful red display in the heavens in terms of theology; instead he accounted for it by the use of the current nitrous-sulphureous theories by which atmospheric phenomena were then explained. Since the preceding days had been hot and sultry, he concluded that the combustible particles had vaporized from the earth, igniting in some manner to cause the fiery exhibition. He regarded the phenomenon as a perfectly natural one and expressed an abhorrence of any prognostications based upon it. Although his scientific interpretation of the aurora borealis would be untenable today, his attitude toward it was indeed a healthy scientific one.

Robie was a Newtonian, and he had learned the new mechanics from such sources as William Derham's *Astro-Theology,* John Keill's *Introductio ad Veram Physicam,* and William Whiston's *Praelectiones Astronomicae.* Robie also made use of the new theories. At the end of his *Almanack* for 1720 there is an appendix containing tables of "The Middle Distances of the Planets from the Sun" and of "The Diameter of the Sun and Planets with the Moon." Robie stated that these tables were ". . . calculated from the latest Observations by Sir *Isaac Newton's* Rules." The publication of astronomical tables computed by "Sir Isaac Newton's Rules" in 1720 is a big advance over the difficulties that Brattle had had with Euclid.

Robie achieved at least a small right to immortality in the field of medicine for his work in connection with the smallpox epidemic of 1721 and 1722. He had educated himself in medicine, as in other sciences, and after Boylston began to inoculate, Robie also adopted the practice, performing the operation on eleven patients. The most complete case histories of those first smallpox inoculations are in Robie's manuscript *Journal of the Inoculation at the Hospital on Spectacle Island.*[30] The first entry in the *Journal* is for May 17, 1722: "Today I went from the College at Cambridge to the Spectacle Island [the isolation hospital in Boston Harbor] to visit the inoculated persons hereafter mentioned, who were by the fury of the Boston mob,

[29] Robie, Thomas: *A letter to a certain gentleman desiring a particular account may be given of a wonderful meteor that appeared in New-England, on December 11, 1719, in the evening.* Boston, J. Franklin for D. Henchman, 1719.

[30] Kilgour, *op. cit.,* pp. 486-87. A copy of Robie's *Journal* in his own hand is in Recompense Wadsworth's MS Commonplace Book at the Massachusetts Historical Society.

forced down to the aforesaid island to go through the operation which was performed on them a day or two before." Robie took care of the six patients on Spectacle Island until June first, when they had all recovered, and his *Journal* for this period shows that he was a very keen medical observer.

His next major investigation, in astronomy, was occasioned by the annular solar eclipse on November 27, 1722,[31] which excited him considerably. He had a wonderful new 24-foot telescope with which to make his observations and he made elaborate arrangements for obtaining as many data as possible. He prepared the people of Massachusetts for the coming phenomenon by his article "For the Entertainment of the Country and the Promoting of Knowledge,"[32] which appeared in at least two Boston newspapers. In this he described the coming eclipse, the extent of which, according to his calculations, would be eleven and a half digits; he also requested that the "curious" make observations and send them to him. When the eclipsed sun rose on the morning of November 27th, Robie was at the 24-foot telescope and his assistant Danforth at the older 8-foot instrument. The event had been so well publicized that most of the members of the College had apparently ascended to the roofs of the buildings, from which vantage point they were able to see the eclipsed sun before Robie. Unfortunately, as in so many eclipses, the sun immediately clouded over, so that Robie was unable to verify his calculations by observing it at its greatest phase. When he saw it again an hour later, it was eclipsed six digits. Apparently in response to his advertisement, he received several observations from others which enabled him to confirm partially his own calculations of the path of the shadow.

In 1723 Robie married and left Harvard to go to Salem, where he practised medicine until his death. At the time of Robie's leaving the college, Harvard's President Leverett recorded in his manuscript "Book Relating to College Affairs"[33] that: "It ought to be Remembered, That Mr. Robie was no small honour to Harvard College, by his Mathematical Performances and by his correspondence thereupon with Mr. Derham & other learned persons in those Studies abroad."

Of the three men—Mather, Dudley, and Robie—who were almost entirely responsible for the sudden rise in scientific activity after 1712, Cotton Mather was the least a true scientist. In fact, he would probably have been

[31] Robie, Thomas: Part of a letter . . . concerning the effects of inoculation; The eclipse of the sun in November 1722; And the venom of spiders. *Philos. Tr. R. Soc. London*, 1724, *33*, pp. 67-70.

[32] *Boston News-Letter*, Nov. 5, 1722, and the *New-England Courant*, No. 67, Nov. 12, 1722.

[33] In the Harvard College Library, p. 252.

surprised to have been called one. Although he was very learned in the scientific knowledge of his day, he made practically no effort to relate observation with theory either by induction or deduction. He was content to send to the Royal Society observations reported to him by his "neighbours," and made almost no direct observations himself. His scientific queries to his informants undoubtedly encouraged an interest in natural phenomena among New Englanders, but it is difficult to judge Mather's position in science fairly. He had never taken the trouble to train himself in the rigorous techniques of scientific observation, so that he lacked a healthy scepticism of the validity of an isolated observation. The result of this want of scientific scepticism is that the majority of Mather's *Curiosa Americana* were valueless as contributions to scientific knowledge and were never published in the Royal Society's *Philosophical Transactions.*

Paul Dudley had more appreciation for the relationship between scientific observation and theory. He was also more sceptical of observations. In his paper on the "Natural History of Whales,"[84] he discussed the origin of ambergris, which was at that time unknown. Dudley described the manner by which a whaling captain had found ambergris in a whale, the story having been told to Dudley by the Reverend Thomas Prince of Boston. Basing his conclusions on the captain's description, Prince was sure that the ambergris came from the urinary bladder, but Dudley, being unwilling to accept outright another's observations, added, "As for my own Part, I dare not pretend to give any opinion upon the Point, but content myself with relating Matter of Fact." Mather was not in the habit of doubting the reports he received.

But whereas Mather and Dudley were amateurs, Thomas Robie was a trained scientist. He was self-taught, it is true, but he was a capable observer and proficient in using scientific theories to obtain an understanding of natural phenomena. His explanation of the aurora observed in 1719 is but one example of his deductive use of scientific theory. As an astronomical observer, Robie was without equal in the colonies, and there were very few colonial physicians who were accustomed to observe their patients as accurately as did Robie.

Robie also played a more important rôle in establishing the scientific tradition in New England than either Mather or Dudley. Isaac Greenwood, who was graduated from Harvard in 1721, undoubtedly owed much of his

[84] Dudley, Paul: An essay upon the natural history of whales, with a particular account of the ambergris found in the sperma ceti whale. *Philos. Tr. R. Soc. London,* 1724-25, *33,* pp. 256-69.

interest in science to Robie. When Greenwood went to London in 1723 to study science, he carried with him a letter from Robie and he subsequently corresponded with him. Greenwood was the first Hollis Professor of Mathematics and Natural Philosophy at Harvard, and in his turn exerted a strong scientific influence on his successor, Professor John Winthrop. Winthrop, who retained this post until his death in 1779, did not have a genius equal to Benjamin Franklin's, but he was the most highly trained and most learned scientist in the colonies and would have been a credit to any eighteenth-century university.

Although it cannot be proved, Robie probably awakened scientific interests in Thomas Clap, who was graduated from Harvard in 1722 and who, as president of Yale from 1740 to 1766, initiated the first vigorous, continuing study of science at the "Collegiate School," as Yale was then called.

Why did the sudden rise in scientific activity occur in the decade following 1712? There was more scientific work done in New England in these years than had been done in the preceding eighty; it was as late as 1705 that Brattle had complained that there was no one who could instruct or assist him in his faltering scientific studies. And where did the scientific knowledge come from that made this new scientific activity possible? No scientists had come from Europe to instruct the beginners; they had of necessity to learn their science from books. But although scientists had not come to New England, letters from members of the Royal Society requesting information undoubtedly stimulated the new scientific activity. As already noted, Cotton Mather's first *Curiosa Americana* were sent off in response to a letter from Dr. John Woodward. When Robie was appointed tutor at Harvard in 1713, he inherited from his predecessor, Edward Holyoke, a correspondence with Matthew Wright of Crew. Wright told William Derham about Robie and it was at Derham's request that Robie maintained a meteorological record of Cambridge weather conditions. Robie also corresponded with Derham about astronomical subjects.

At the beginning of the eighteenth century, Boston's population was less than 10,000, but it was growing rapidly; urban intellectual companionship was increasing, and schools becoming more numerous. New England was beginning to prosper, and her people consequently were beginning to enjoy a greater degree of economic security than formerly. These social factors probably had an indirect effect in encouraging scientific activity.

But the factor of human curiosity must not be neglected. Even in the most favorable social circumstances, there would be no active science without curiosity about nature. There are, of course, many ways of expressing

intellectual curiosity other than seeking the knowledge called science. Seventeenth-century New Englanders had been almost exclusively engaged in seeking knowledge and truth in the realm of theology. It seems very unlikely that they became interested in scientific pursuits merely because of the change in social climate. It is much more likely that the tremendous increase in scientific activity in seventeenth-century Europe was the most influential factor. Theological pursuits had already trained the New England mind to rigorous thinking, and when the stimulating books of Newtonian science arrived in New England, the colonists read them and accepted the new "philosophy." Mather, Dudley, and Robie not only read the new science, but, their curiosity having been directed into fresh intellectual channels, they also began to make original investigations. Robie in particular adopted the new scientific mode of thought.

The beginnings of New England science that have been described in this paper were faltering and uneven in quality. The great importance of Mather, Dudley, and Robie is that they were the "beginners." Only in the light of subsequent history of science in America can their pioneer efforts be appreciated. If questions are raised as to the value of their early work, the best reply is one of the famous responses of a later colonial scientist, Benjamin Franklin: "What good is a new-born baby?"

TOXIC EFFECTS OF ANTITHYROID DRUGS*

J. P. PETERS, E. B. MAN, D. M. KYDD, W. W. ENGSTROM, AND L. L. WATERS

The first studies on thiourea in this department were undertaken for reasons quite apart from the purposes for which it is now used. It had been reported that this compound distributed itself uniformly throughout the fluids of the body, that it was excreted like urea and could be recovered in the urine, completely, unchanged.[31] These characteristics, if they could be verified, would make thiourea an ideal means of measuring the total volume of water in the body. When the subject was investigated by Purple and Lavietes,[35] it was discovered that large doses of thiourea, 6 to 10 gm., induced severe nausea and vomiting with malaise, but no other discernible symptoms. Measurements of its volume of distribution and excretion yielded values that lent plausibility to the idea that it diffused freely through all the water and escaped destruction. Subsequently it was found that in somewhat smaller doses it produced offensive halitosis.

Because of its untoward effects it was evident that the compound must be given in smaller doses if it was to be used for physiological studies. This required the development of a more sensitive analytical technique. A procedure was, therefore, devised which permitted measurements of the desired accuracy when doses of about one-tenth the former magnitude were used.[11] When such doses, 0.5 gm., were injected into dogs, it proved impossible to recover the whole of the injected dose in the urine.[12] A small fraction appeared to be disposed of in some manner. This had not been detected in the earlier studies because this fraction was so small in proportion to the large doses that had been given. With this quantity of thiourea the dogs, with the exception of one which invariably vomited, exhibited no untoward signs or symptoms, and postmortem examinations of animals who died from other causes incident to the experiments revealed no lesions that could be attributed to any untoward actions of the drug. Obviously thiourea was unsuited to the purpose for which it had been intended—measurement of the total fluid of the body. It could be inferred from its incomplete recovery

* From the Departments of Internal Medicine and Pathology, Yale University School of Medicine. This investigation was aided by grants from the U. S. Public Health Service and the Fluid Research Fund, Yale University.

Received for publication April 29, 1949.

and the fact that large doses had a toxic action that the compound was not physiologically inert nor altogether unchanged in the body. Nevertheless, it seemed to have been established that single doses of moderate size had no deleterious effects. To make assurance doubly sure, some time later a number of patients were given intravenously test doses of 0.4 to 1.0 gm. The largest dose occasionally caused mild nausea or vomiting.

The latter part of this work coincided with the appearance of reports that thiourea and other drugs containing sulfur in a similar linkage produced in animals goiters with hypothyroidism. One of these, thiouracil, had been employed for the treatment of hyperthyroidism with reported success. Thiourea had been rejected for two principal reasons. In rats, large doses of the compound had been found to precipitate fatal pulmonary edema with pleural effusions. In addition, experiments with certain species of animals had indicated that it had less goitrogenic activity than thiouracil did.[2, 4, 5, 48] In spite of these adverse decisions it was decided to use thiourea for a study of the medical treatment of hyperthyroidism. Since an accurate method for its measurement in body fluids was available, its metabolism could be studied. The experiments cited above had proved that doses of the size contemplated for therapeutic use provoked neither in man nor dogs the disorders that larger doses had produced in rats. The incidence of these acute lesions in rats had proved to be peculiar and capricious, susceptibility varying with age, diet, and variety.[1, 16, 17, 18, 22, 28] In most other species tested the compound had proved innocent. Astwood[2] has stated that thiourea is the least toxic of a large number of effective drugs which he tested. In dogs, doses which had no detectable evil effects depressed thyroid activity.[14] It was soon demonstrated that it was equally effective in low dosage as an antithyroid agent in patients with hyperthyroidism.[18] It was conceived that thiourea, being chemically the simplest member of its group, might display the action of the thio-linkage with a minimum of side effects. Reports of agranulocytosis and its attendant disorders, from thiouracil, had already begun to appear. The presence of a ring in thiouracil, it was argued, might well provoke agranulocytosis, whereas thiourea, without a ring, might not.

Certain other decisions were reached at the same time: (i) that iodine in therapeutic doses should be given with thiourea; (ii) that the policy of giving no barbiturates or other sedative drugs, with the occasional exception of soporific doses of chloral hydrate, should be followed more rigorously than before. Iodine was given to allay any possible goitrogenic action of thiourea and to accelerate its antithyroid effect. It had been claimed by numerous observers[8, 9, 19, 21, 25, 34, 37, 42, 44] that preliminary treatment with iodine

delayed or even inhibited the action of thiouracil. The evidence to this effect was not altogether convincing. On theoretical grounds, it seemed illogical that they should be antagonistic, since in hyperthyroidism both drugs, though differing in their mode of action, had an inhibitory effect. The use of barbiturates in the treatment of hyperthyroidism has been generally discouraged because it is felt that their depressing effects are not beneficial to patients with this condition. They were prohibited in the series treated with thiourea lest they confuse the issue. If they were given, it would be impossible to distinguish with certainty whether rashes, agranulocytosis, and other toxic manifestations were caused by thiourea or barbiturates. This point has been too often overlooked. Many reports of intoxication from thio-drugs can not be properly evaluated either because barbiturates were given or because it was impossible to ascertain from the reports whether or not they were given. As far as possible in this series other drugs which could cause similar confusion were avoided.

As means of checking the effects of therapy, chief reliance was placed upon periodical measurement of the precipitable iodine of the serum, SPI.[20] Basal metabolism was also determined in most cases and, in a certain number, serum lipids as well. The present communication deals with possible toxic effects of thiourea.

In one respect the course which was elected has been justified. Evidence has been adduced that the actions of iodine and thiourea are not antagonistic.[13, 15] By the initial use of iodine, hyperthyroidism may be partially alleviated before the effect of the slower-acting thiourea is attained. Iodine also appears to augment the effect of thiourea. Continuous use of the two drugs in combination, therefore, permits control of hyperthyroidism with smaller doses of thiourea than would otherwise be necessary. This must diminish the danger of any toxic action that the thio-drug might exert. The experience of Rawson and associates[30] agrees with our own in these respects. As far as the antigoitrogenic action of the iodine is concerned, no opinion can be given. In no case was there any evidence that thiourea given with iodine had a goitrogenic action. In the few patients who came to operation after this therapy, the thyroid glands did not appear to be more vascular or hyperplastic than glands from subjects who had been prepared for operation by iodine alone. This evidence must be discounted, however. Although it has been established that thio-drugs have a goitrogenic action on euthyroid animals, there is no indisputable evidence that they have a similar effect on the glands of patients with hyperthyroidism. Many have reported diminution in the size of the hyperthyroid gland under the influence of thio-drugs,

though sometimes after a preliminary swelling. This latter phenomenon is, however, occasionally observed when iodine is used. Lahey and his associates[25] have emphasized the great vascularity of glands after treatment with thiouracil alone. Although they believe that iodine retards the action of thiouracil when the two are given together initially, they are convinced that it reduces the vascularity of the gland if given for two or three weeks before operation after the effect of thiouracil has been obtained. Enlargement of the thyroid gland is likely to occur if combined iodine and thio-drug therapy is pushed to such a point that it produces myxedema. An example of this is cited below.

Evaluation of the relative antithyroidal activity of the various thio-drugs has not been entirely satisfactory. The majority of pharmacological studies have employed as their sole criterion the degree of hyperplasia of the thyroid gland of rats. On the basis of such assays Astwood,[1] who has made the most intensive investigation, estimates that 0.6 mg. of thiouracil is as effective as 2.1 mg. of thiourea, while 6-propylthiouracil is still more potent. On a molecular basis this would mean that thiouracil is six times as effective as thiourea. In most of these assays thiourea has been treated rather cavalierly or neglected. The few who have employed the compound therapeutically seem to have taken it for granted that these assays apply to man and have usually used 1 gm. or more per day in a rather arbitrary manner, to the discredit of the compound.[2, 20, 26, 33] For example, Morgans[33] used 3 gm. per day, in contrast to 0.6 to 1.0 gm. of thiouracil and 0.6 gm. of methyl thiouracil and aminothiazole. Ritchie and Geddes[39] used from 2 to 5 gm. per day. Such large doses invariably produced objectionable halitosis and other untoward symptoms and signs. In a preliminary evaluation of the drug, Winkler, Man, and Danowski[47] showed that doses as small as 70 mg. daily produced or maintained a remission in hyperthyroidism with considerable regularity, and that as little as 25 to 50 mg. daily sometimes maintained such a remission. The drug was used by them in conjunction with iodine, which augments its action. Further experience has proved that the required dose varies from these small amounts to about 210 mg. daily. A few patients have been found who did not respond completely to this large dose—or rather, who at times could not be controlled with such a dose. This will be the subject of a separate report. The point is brought up now to emphasize that, gram for gram, thiourea appears from our experience to be more effective than other thio-drugs that have been widely used. If, however, the action of these drugs depends upon the thio-linkage, they should be rated not according to actual weight, but according to the quantity of sulfur they

contain. The molecular ratio, thiourea : propylthiouracil = 76 : 170 = 0.45. On this basis thiourea should be roughly twice as effective, gram for gram, as propylthiouracil. In estimating both its effectiveness and its toxicity, this must be taken into account. In evaluating toxicity this is particularly important, because only by making the comparison on this basis will it be possible to distinguish whether an unfavorable reaction should be ascribed to the thio group, to the whole class of drugs, or to a particular member of this class.

Toxic or untoward reactions

The chief untoward effects that have thus far been reported from the therapeutic use of thio-drugs are: (i) febrile reactions, (ii) skin rashes of various kinds, (iii) leucopenia and agranulocytosis, (iv) muscle pains, arthralgia, and arthritis, (v) miscellaneous disturbances of the gastro-intestinal tract, genito-urinary tract, liver, etc. These last have been so occasional that it is quite uncertain whether they can always be related directly to the drugs to which they have been attributed. Some of them may be referable only to particular drugs. Our attention will be confined chiefly to the first 4 types of reactions.

In one respect thiourea appears to be distinguished from all of the other drugs of its class that have as yet been employed for therapeutic purposes. Approximately 300 cases have now received the compound for the treatment of hyperthyroidism in this clinic for periods up to almost 4 years without a single instance of agranulocytosis or significant leucopenia. Blood counts were made with great frequency on all cases for a long period and are still made at sufficiently frequent intervals to assure us that reductions of leucocytes have not escaped our attention. Two cases have been mentioned by Ritchie and Geddes.[39] One, from their own series, developed agranulocytosis after 3 months' treatment with extremely large doses of thiourea. The other case they cite by courtesy of another physician without details. Leucopenia and agranulocytosis have occurred with varying frequency after therapeutic doses of all the members of the thiouracil group: thiouracil,[2, 23, 24, 32, 41, 45] thiobarbital,[6, 10] 6-propylthiouracil,[27] 5-methylthiouracil,[7, 20, 26] and others.[43] The cases of Ritchie and Geddes[39] cast doubt upon the presumption that the absence of a ring form would preclude this complication. Dosage may play its part. Thiourea does appear to have less tendency than the thiouracils to produce leucopenia and agranulocytosis.

Altogether 35 patients at one time or another in the course of treatment

with thio-drugs, chiefly thiourea,* developed complications of some kind. These patients and their records have been carefully scrutinized to ascertain whether these disorders could be attributed to toxic effects of the thio-drugs. All those in which there was reasonable suspicion are discussed in this report, even though the evidence against thiourea is quite tenuous in certain cases. In 17 of the 35 cases thiourea could be clearly exonerated; in 6 it was as clearly convicted. The remaining 12, of whom 5 died, will be the chief subjects of discussion in this paper.

One patient developed urticaria which seemed to be directly referable to thiourea. A woman of 45 with Graves' disease of 2 months' duration had a basal metabolism of +32 per cent and a serum precipitable iodine of 11.4 γ per cent. On 15 drops of Lugol's solution and 15 mg. of thiourea daily, basal metabolism and serum iodine became normal and symptoms disappeared in 6 months. After 10 months, medications were stopped. Four months later they had to be resumed because of a relapse, and after another 2 months the thiourea was increased to 25 mg. daily. After she had taken the drug daily, with the exception of the intermission mentioned above, for 22 months, she developed urticaria which ceased within 24 hours after she stopped the thiourea. On 2 subsequent occasions, at intervals of about 5 days, small single doses of thiourea precipitated attacks of urticaria which each time lasted only 24 hours. Propylthiouracil in the same dosage provoked no such reaction, but did not control the hyperthyroidism completely, as evidenced by a continuous slight elevation of the serum iodine. The urticarial reaction in this case appeared to be specific for thiourea, although this can not be asserted with certainty since the dose of propylthiouracil with which the thiourea was replaced contained only half as much sulfur. Furthermore, this reaction came on, as similar reactions to insulin sometimes do, while the subject was receiving continuously doses of the drug that should have desensitized her. It is possible that, had thiourea been continued, the urticarial reaction would have ceased as the urticarial reactions to insulin usually do. Since a substitute was available, this rather trying process was not tested.

No other urticarial rashes, no exfoliative nor other types of generalized dermatitis have occurred. Certain peculiar skin disorders will be mentioned below in another connection.

In two instances the drug was discontinued because it produced nausea. The first, A22701, a woman of 53, in 1943 was given 1 gm. of thiourea

* Thiourea was most frequently implicated because at the time of this study it was almost exclusively employed.

daily. This caused severe nausea and was, therefore, discontinued within a week. The nausea in this case was due only to excessive doses of the drug; it can be ascribed to inexperience and discounted. The second patient, B74809, born in 1883 (a sister of B73276, who is mentioned below as having had an early febrile reaction), had a thyroidectomy for hyperthyroidism in 1930. She came to the clinic December 24, 1945, two weeks after an anginal attack, with symptoms and signs of hyperthyroidism and a blood pressure 190/100. She had been taking 10 drops of Lugol's solution daily since her previous operation and had been digitalized at the time of her anginal attack. On December 17 the basal metabolism was +17 per cent, SPI 12.0 γ per cent. She was given 15 drops of Lugol's solution and 75 mg. of thiourea, which was increased to 210 mg. daily 3 days later. Because of nausea and vomiting this was reduced to 25 mg. on January 18, although SPI was 11.3 γ per cent. Subsequently, because she failed to improve, the dose was increased successively to 50, 75, and 100 mg. Nausea again compelled reduction of the dose to 75 mg. On this the basal metabolism and pulse were controlled, but SPI remained consistently elevated and symptoms did not seem to be allayed. On August 3 the dose was again raised to 100 mg., and again nausea appeared after a few days. For this reason on August 21, 100 mg. of propylthiouracil daily was substituted. This did not provoke nausea. In this case the nausea seemed to be directly referable to intolerance for thiourea and related to the dose of the drug. It was associated with no other symptoms and no objective signs. It may have represented merely an aversion to the drug.

Three patients have had simple febrile reactions. These appeared on the 7th, 9th, and 13th days of medication with thiourea, respectively. The first two patients had received 210 mg., the third 70 mg., daily. In every case the temperature fell rapidly after the drug was discontinued and rose sharply when it was given again. The only associated symptom was general malaise. In every instance the drug was discontinued. One of the patients was subjected to thyroidectomy. Febrile reactions of this type have been described after all the thio-drugs: thiourea,[20, 33] thiouracil,[23, 24, 26, 32, 41, 45] thiobarbital,[6, 10] 5-methylthiouracil,[7, 20, 26, 43] propylthiouracil,[38] and others.[43] They usually appear, as these did, within 7 to 14 days after initiation of therapy. Presumably, therefore, they are manifestations of sensitization to these compounds. They may be induced by small doses as they were in the last of our cases; but they are more frequently provoked by large doses. Morgans,[38] for example, reports 6 febrile reactions of this type in 7 cases who received 3 gm. of thiourea daily. This suggests that their frequency might be reduced

to a minimum by the use of small doses for the first 2 or 3 weeks of treatment. Although early febrile reactions have been induced by all the thio-derivatives and may, therefore, be regarded as one of the generic responses to these drugs, they are not altogether non-specific. A large proportion of patients do not respond with fever when another compound is substituted, though this is not always the case.[3, 10, 24, 38, 48] This was not tested on any of the patients in this series. Nor was the drug continued in spite of the fever as it has been by some clinicians who claim that this is a self-terminative type of reaction. It has not seemed justifiable to us to continue a therapeutic procedure in the face of such untoward reactions when there are alternate courses to pursue. Desensitization by small doses has not been attempted.

In most reports no distinction has been drawn between these early febrile reactions and later febrile disorders. In our experience the patterns of the two differ. Arthritis, myalgia, and other disorders of the musculo-skeletal system have been reported as occurring with varying frequency in the course of treatment with all of the thio-drugs.[20, 23, 26, 27, 43, 45] Nevertheless, no accurate descriptions of these disorders nor their relation to therapy can be found in the literature. To us they have seemed to merit particular attention. Polyarthritis, even if it appears to be rapidly self-terminative, is not a condition that can be lightly regarded in view of our present concepts of rheumatic and rheumatoid affections. The association of myalgic pains, rashes, and fever, quite casually mentioned in many reports, should cause some anxiety. In this spirit we have followed with great care and no little bewilderment the course of all febrile complications occurring during thiourea therapy. Every effort has been made to ascertain whether such complications could be related to the therapy, frequently with baffling results. These studies are the chief theme of this report. Altogether, 12 patients had late febrile disorders, usually accompanied by pains in the muscles or joints, sometimes by obvious arthritis, and by peculiar multiform skin lesions. Five of these patients died and autopsies were obtained on all. Protocols of all are presented, because only by such a comparison can the relation of their disorders to the drug be properly evaluated.

B45335 (JN), female, born in 1875, according to her record had partial thyroidectomy in 1895 (the date must be erroneous) for hyperthyroidism of two years' duration, with only partial relief of symptoms. Emotional and exertional palpitation and excessive sweating persisted and the goiter enlarged. In 1930 she was institutionalized for a nervous breakdown. In 1944 she developed conjunctivitis and increased intraocular tension. In 1945, with buzzing in her head, hypertension was discovered. When seen in the dispensary, September 28, 1945, she was sweating, nervous and tremulous, with pulse 132, blood pressure 215/120, moderate exophthalmos, bilateral lenticular opacities,

a low midline goiter, and a slightly enlarged heart with an aortic systolic murmur. Six weeks later her basal metabolism was +24 per cent, SPI 8.3 γ per cent.

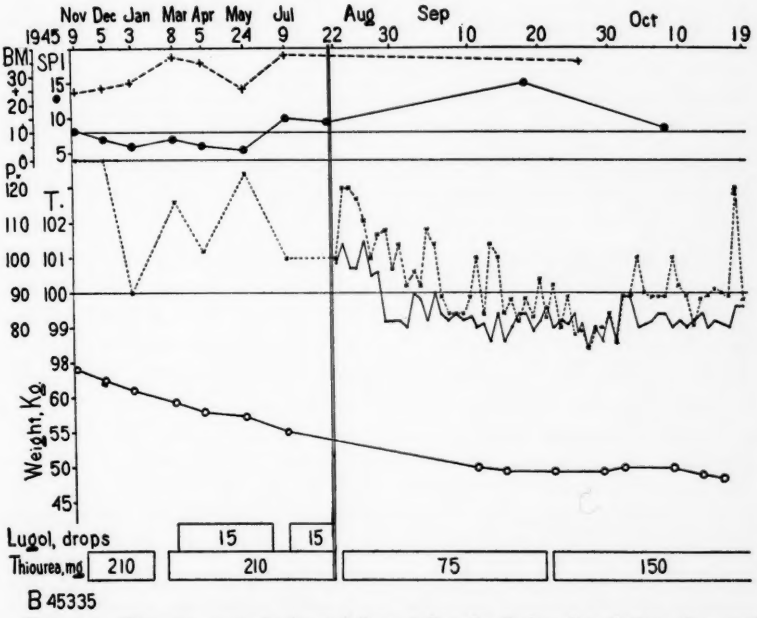

CHART 1. The two upper horizontal lines define the limits of variation of normal SPI, the lowest horizontal line the upper limit of normal rectal temperature. The time scale is contracted during the period to the left of the double vertical line, while the subject was not in the hospital.

Her course is illustrated in Chart 1. Thiourea (210 mg. daily) was continued (with the exception of 2 weeks at the end of January, 1946) until her admission to the hospital on August 22. Early in March, 15 drops of Lugol's solution daily were added. The serum iodine responded promptly, but basal metabolism and pulse remained elevated. May 24 nocturnal dyspnea and inability to lift the right arm were reported. Though there was no edema, hepatic enlargement, nor pulmonary congestion, digitalis was given. July 9 SPI had risen and basal metabolism reached a new high. Iodine had been discontinued for a short period before this, but its resumption did not check the rises. August 19, after an upper respiratory infection, she developed arthritic pains. August 22 she was admitted to the hospital with temperature 102.4°, swelling, tenderness and pain in both knees and the right ankle, and pain on motion of several other joints. Heart and liver were both enlarged, but lungs were clear and there was no edema. The dose of thiourea was at once reduced and for Lugol's solution there was substituted KI, which was discontinued 5 days later. August 24 the submaxillary

glands became swollen and tender. August 25 she had pleuritic pains. Her temperature subsided after about a week, the pulse rate decreasing at the same time; but the joint pains persisted with diminishing severity until October 10. X-rays on September 12 and at intervals thereafter revealed pneumonitis of both lower lobes and a pleural effusion on the right, but no fluid could be obtained on repeated attempts at thoracentesis. On one occasion a transient papulovesicular eruption appeared on her elbow. Because SPI had risen to 13.9 γ per cent on September 18, thiourea was increased to 150 mg. daily. She continued afebrile, her symptoms disappeared, and the SPI fell on this regime. The blood count remained normal throughout the course of her illness. In addition to the disorders already described, x-ray revealed hypertrophic osteoarthritis, generalized osteoporosis and posterior dislocation of the 5th cervical vertebra on the 4th. On October 10 a fracture of the 8th rib in the mid-axillary line was also discovered. The patient did not return after her discharge from the hospital.

There are several puzzling features in this case, the first being the discrepancy between pulse and basal metabolism on the one hand and SPI on the other during the early part of her course, when her weight was declining steadily. If the rise of SPI in July had been referable to withdrawal of iodine, it should have fallen again instead of rising when iodine was resumed. The increases of both SPI and basal metabolism at this time may have been connected with the complicating condition that later manifested itself as arthritis. The subsidence of the arthritis when the dose of thiourea was reduced may have been only a coincidence, since it continued to subside when the dose was again raised to 140 mg. per day. What might have happened if it had been raised further to the original 210 mg., it is impossible to say. Since the SPI appeared to be falling and symptoms were diminishing on 140 mg., the effect of a larger dose was not tested. On the whole the patient could not be convicted unequivocally of thiourea intoxication.

B73533 (ES), female, born in 1876, had typhoid fever in 1890, broke her hip in 1941, and in the same year had a cholecystectomy and a hernioplasty. In 1944 she had a hemorrhoidectomy. In 1942, exertional dyspnea, palpitation, and edema began. From about 1931 her tongue had been sore. At the end of 1944 anorexia and frequent headaches set in. Between 1942 and 1945 her weight fell from 226 to 135 pounds. In March or April, 1945, she began to have difficulty swallowing solid food. In June, diagnoses of esophageal diverticulum and hyperthyroidism were made. She was admitted to the New Haven Hospital on October 19, extremely wasted, with an enlarged thyroid, pulse 82, blood pressure 164/74, enlarged fibrillating heart, slightly enlarged liver, edema of the legs, a slight cystocele, and a red tongue with smooth edges. Her chief complaints were dysuria and diarrhea. The stools were reported as distinctly fatty and x-rays revealed osteoporosis. A low-grade temperature, attributed to urinary tract infection, was treated with penicillin. X-ray also revealed a pulsion diverticulum of the esophagus. Early in November the basal metabolism was found to be +29 per cent. SPI 21.4 and 18.1 γ per cent. Her course is illustrated in Chart 2.

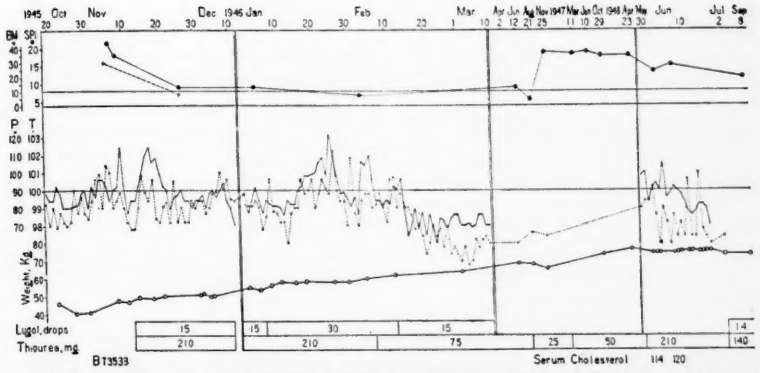
1945 Oct Nov Dec 1946 Jan Feb Mar Apr Jun Aug Nov 1947 Mar Jun Oct 1948 Apr May Jun Jul Sep
BM SPI
P T
Weight, Kg.
Lugol, drops
Thiourea, mg.
BT3533
Serum Cholesterol 114 120

CHART 2. The two upper horizontal lines define the limits of variation of normal SPI, the lowest horizontal line the upper limit of normal rectal temperature. The first double vertical line represents an interval when the patient was not in the hospital and not observed. Between the second and third double vertical lines, while the subject was an outpatient, the time scale is contracted.

On November 12, just after her temperature had become normal, she was started on 210 mg. of thiourea and 15 drops of Lugol's solution daily. Three days later the temperature rose again. Because the urine was found to be infected she was given sulfadiazine. The temperature ceased after about 10 days, to recur a little later, when penicillin was again given. December 9, when the basal metabolism had fallen to +8 per cent and SPI to 9.2 γ per cent, both thiourea and Lugol's were stopped.

She was discharged from the hospital on December 13. Just before this dysuria and frequency occurred; by the end of the month, they had become so severe that she was readmitted December 31. She was given 420 mg. of thiourea that day and thereafter 210 mg. with 15 drops of Lugol's solution daily. She also received sulfadiazine for a few days. By February 4 SPI had fallen to 6.7 γ per cent; but irregular bouts of fever continued and the urinary infection persisted. February 12 a colpoperineoplasty was performed because the cystocele was believed to be responsible for the persistence of the cystitis. The thiourea meanwhile had been reduced to 70 mg. daily. She remained in the hospital until March 10, afebrile and free from symptoms.

For some time after discharge she remained relatively free from symptoms, though SPI was elevated. October 29, 1947, a brawny, erythematous patch appeared on her right thigh and she complained of pulling and soreness in the right upper quadrant of her abdomen. The liver edge was down 2 to 3 fingerbreadths. On the earlier admissions some evidences of impaired liver function had been noted. April 23, 1948, she had recurrent chills and sweats and occasional right upper quadrant pain which, she said, resembled an attack she had had 30 years earlier. Meanwhile, despite the high SPI, the thiourea had been reduced to 25 mg. daily. May 29 she was admitted to the hospital with herpes zoster of the right supraorbital region. Since her earlier admissions she had gained much weight. She was again given 210 mg. of thiourea daily. The temperature on admission and for the next 10 days was slightly elevated, but returned to

normal on June 9, 2 days before thiourea was discontinued in spite of a persistently high SPI. The patient did not appear hyperthyroid, although she perspired rather profusely. Her serum cholesterol was, however, persistently low. The blood pressure was normal after the first admission. The blood count remained normal throughout her illness.

After discharge she took thiourea and iodine irregularly. July 2 she was complaining of intermittent pain in the right side of the abdomen. She did not seem hyperthyroid. September 8, having taken 140 mg. of thiourea and 15 drops of Lugol's solution daily meanwhile, SPI was 11.8 γ per cent, though symptoms of hyperthyroidism were minimal. November 17, on the same medication, recovering from a mild coryza, she complained of slight swelling in the submaxillary region for a month. No objective equivalent was noted. Her skin seemed slightly dry, but there were no other evidences of hyperthyroidism.

The fever in this case can not be indisputably attributed to thiourea. Although at times the two seemed to be correlated, this relation was inconsistent. In every instance some entirely unrelated cause could be found for the fever. The SPI remained consistently elevated without comparable clinical signs of hyperthyroidism. It can not, however, be altogether discounted; it was associated with low serum cholesterol. The pulse was misleading because of the presence of fibrillation. Even at the height of her hyperthyroidism, when the basal metabolism was +29 per cent, the pulse rate was only 82.

B90726 (MS), female, born in 1886, was first admitted to the hospital March 28, 1948, because of an attack of acute pulmonary edema. She had had hypertension for 5 or 10 years and anginal attacks for 1 year. She was poorly nourished, acutely distressed and apprehensive, with pulse 96, blood pressure 180/90, heart greatly enlarged and fibrillating, fine moist râles at the bases of both lungs, enlarged liver, and slight pitting edema of the legs. Her skin was notably soft and smooth and she had a nodular goiter of moderate size. She was given digitalis and subsequently quinidine for recurrent episodes of rapid fibrillation. On March 31 her SPI was found to be 13.0 γ per cent. Her subsequent course is illustrated in Chart 3.

Lugol's solution, 20 drops daily, was begun on April 1 and on April 8, 75 mg. of thiourea were added. On this regime she improved markedly. April 30 the thiourea was increased to 140 mg. May 16 she developed stiffness in her neck and pain in her knee. When admitted to the hospital on May 19 her temperature was 101.2°, pulse 112, blood pressure 224/124 to 168/90, her neck was held stiffly, the heart was enlarged with a variable rhythm, the lungs were clear, the left knee was swollen and warmer than the right. In the course of the day the temperature rose to 104.2°, the pulse to 140. Spinal fluid and cultures of blood and urine were negative. Her leucocyte count was 24,000 with 80 per cent of polys; her urine contained a trace of albumin. The throat culture yielded a heavy growth of β-hemolytic streptococci. SPI on May 21 was only 6.7 γ per cent. Thiourea was discontinued for 2 days and then resumed in doses of 75 mg. daily. Penicillin was given. The temperature and tachycardia continued, though gradually diminishing, through June 10. The thiourea was discontinued on June 3,

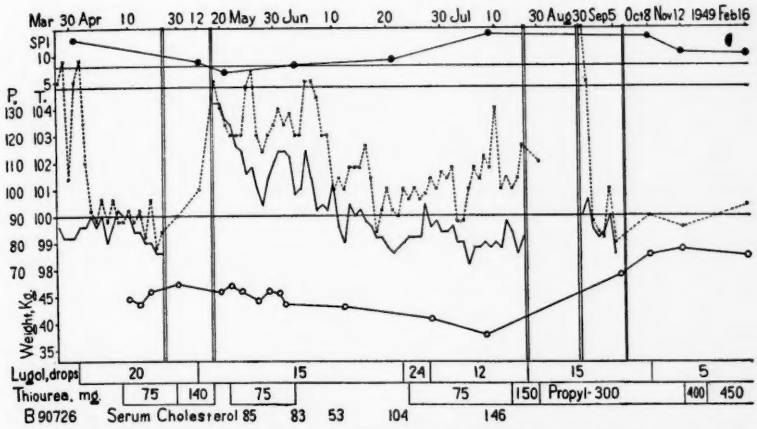
Mar 30 Apr 10 30 12 20 May 30 Jun 10 20 30 Jul 10 30 Aug 30 Sep 5 Oct 8 Nov 12 1949 Feb 16
SPI
P. T.
Weight, Kg.
Lugol, drops 20 15 24 12 15 5
Thiourea, mg. 75 140 75 75 150 Propyl-300 400 450
B 90726 Serum Cholesterol 85 83 53 104 146

CHART 3. The two upper horizontal lines define the limits of variation of normal SPI, the lowest horizontal line the upper limit of normal rectal temperature. During the second, fourth and sixth of the periods separated by double vertical lines, while the subject was an outpatient, the time scale is contracted.

pyribenzamine being given. Shortly after admission the liver was found to be considerably enlarged and tender, serum cholesterol extremely low with an increased ratio of free to total cholesterol, and cholesterol flocculation 4+, suggesting profound disorder of liver function. After her temperature became normal her pulse remained elevated, her appetite poor, and wasting continued. SPI on June 21 was 9.2 γ per cent so thiourea was resumed. She took 75 mg. daily until July 12 without recurrence of fever. At that time, because wasting continued and the SPI had risen to 13.9 γ per cent, the dose was increased to 150 mg. daily. On July 30, although she was steadily improving and there were no signs of intoxication, she was changed to 300 mg. of propylthiouracil.

She was doing well on this regime at home until she stopped taking digitalis. August 30 she was again admitted to the hospital in a state of acute pulmonary edema which cleared rapidly upon resumption of digitalis. She was discharged again on September 6. While in the hospital she was given on two successive days, without reaction, 75 and 140 mg. of thiourea respectively. On this admission she again had a polymorphonuclear leucocytosis. After discharge, on digitalis, Lugol's solution, and propylthiouracil she did remarkably well; but it was necessary to increase the dose of propylthiouracil to 400 and then 450 mg. daily because of a rising SPI and recurrent symptoms of hyperthyroidism. While in the hospital on both second and third admissions she had slight glycosuria at times and postabsorptive hyperglycemia on several occasions. In the latter part of 1948 constant glycosuria, persistent hyperglycemia, and diabetic symptoms compelled administration of insulin. On October 14 she was given, for test purposes, 210 mg. of thiourea with an additional 70 mg. the next morning. This did not provoke fever or any other untoward reaction.

In this case no clear connection could be established between the thiourea

and the arthritis, which seems to have originated from a hemolytic streptococcal infection of the throat.

B73103 (MJS), female, born in 1874, had had one pregnancy which ended in early abortion. She had suffered from urinary frequency without dysuria for many years. In 1936, because she was suspected of hyperthyroidism, she was given iodine for several months. About the middle of 1943 nervousness, irritability, and loss of weight began. When seen in June, 1944, she had definite exophthalmos, the characteristic skin texture and moisture, tachycardia, tremor and enlargement of the thyroid. The heart was overactive, but not enlarged, the lungs clear, the liver down 5 cm. There was no edema. The basal metabolism was +43 per cent, SPI 8.9 γ per cent. Her course is illustrated in Chart 4.

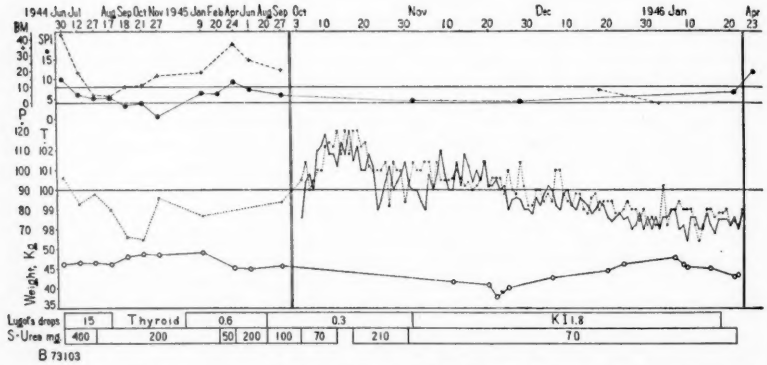

CHART 4. The two upper horizontal lines define the limits of variation of normal SPI, the lowest horizontal line the upper limit of normal rectal temperature. During the period to the left of the double vertical line, while the subject was an outpatient, the time scale is contracted.

She was given daily 15 drops of Lugol's solution and 400 mg. of thiourea, which was reduced to 200 mg. about a month later when the basal had fallen to +5 per cent, SPI to 5.2 γ per cent, and symptoms of hyperthyroidism had ceased. Shortly after this Lugol's was discontinued. In September the SPI had fallen to 3.3 γ per cent, in October her eyes were puffy although the basal metabolism was still +11 per cent; in November she was definitely myxedematous with SPI 0.6 γ per cent, although the basal metabolism was +17 per cent. When thyroid was given without discontinuing thiourea, the basal metabolism rose to +37, SPI to 9.3 γ per cent, and her weight fell. Five weeks later doses of both thyroid and thiourea were halved. By the end of September, 1945, the basal metabolism had fallen to +21 per cent, SPI to 6.0 γ per cent. Meanwhile, as early as July, while she was still receiving 200 mg. of thiourea daily, painful red spots which tended to ulcerate had appeared about her ankles, accompanied by a slight temperature.

She was admitted to the hospital October 4, poorly nourished, with slight exophthalmos, pulse 96, blood pressure 144/80. There were small ulcerative lesions over the feet and the lower parts of the legs, surrounded by erythema. Cultures from these lesions as well as the blood were negative, as were agglutinations of all kinds. She had some evidence of impaired liver function and a polymorphonuclear leucocytosis that rose as high as 16,000. Discontinuation of both thiourea and thyroid from October 12 to 19 had no apparent effect on fever or skin lesions. At the end of this period thiourea was resumed in higher dosage, this time with Lugol's solution. The thiourea was again reduced to 70 mg. on November 7 because SPI had fallen to 4.6 γ per cent. November 25 the temperature fell and remained normal thereafter, with the exception of 2 days, despite continuation of thiourea, until her discharge on January 27, 1946. By that time all the skin lesions were healed. She was followed in the dispensary until April 23. At this time SPI had risen to 11.7 γ per cent. Presumably 70 mg. of thiourea were insufficient. She was not seen again. It was learned that shortly after her last visit to the dispensary she fractured her femur (x-rays in the hospital had revealed general osteoporosis).

This case is peculiarly baffling. It is reported that at the onset her rash cleared when she discontinued thiourea for a short time, but there were no observations to support this. At the time of admission she had received only small doses of the drug, or none for a considerable interval. In the hospital interruption of the drug for a week had no demonstrable effect. Increasing the dose to 210 mg. daily was equally ineffective so far as the rash was concerned, though it did reduce basal metabolism and SPI. Rash and temperature ultimately subsided under the same dose of thiourea with which they began.

C2869 (AM), female, born in 1896, had anterior poliomyelitis in 1906. In 1925, because of a residual deformity, her Achilles tendons were lengthened. Since that time her ankles have been large. She suffered from hay fever. Some time in 1945 she noted a swelling in her neck and began to lose weight. When first seen on September 11, 1946, she had ruddy, moist skin, no exophthalmos, enlargement of the thyroid, pulse 106, blood pressure 152/88, an enlarged heart with a harsh precordial systolic murmur, and large shapeless legs that did not pit. The basal metabolism was +40 per cent. SPI was 8.4 γ per cent. Her course is illustrated in Chart 5.

She was given daily 15 drops of Lugol's solution at once and 75 mg. of thiourea a week later. Because she did not respond, the dose of thiourea was increased successively to 140 and, on August 7, 1947, to 210 mg. At this time, following a sore throat, SPI had risen. On the higher dose, by September 24, nervousness had diminished. A week later she noticed the gradual onset of malaise, chilly sensations, generalized aching and feverish feelings, occasional frank chills. About the same time a rash appeared on both ankles. She was admitted to the hospital on October 6, flushed and hot, with throat injected, a few petechiae on her hard palate, slight bilateral costovertebral tenderness, slight pitting edema of both legs and ankles, a petechial rash extending from the ankles to the middle of the legs, temperature 102.4°, pulse 108, blood pressure 150/100. The blood culture was negative, the throat culture innocent.

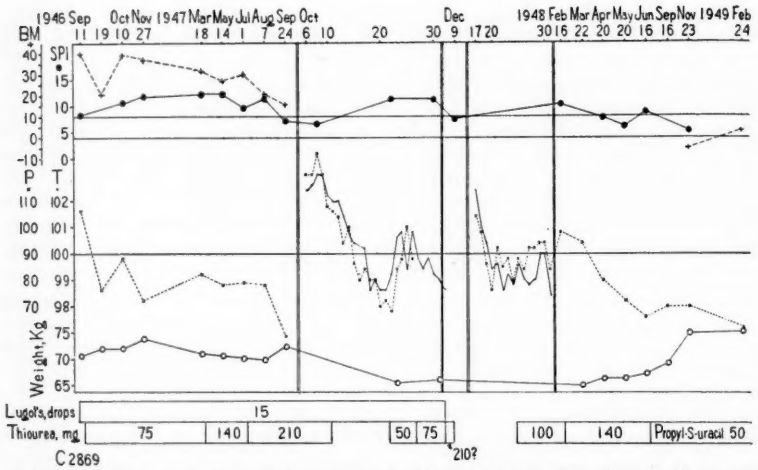

CHART 5. The two upper horizontal lines define the limits of variation of normal SPI, the lowest horizontal line the upper limit of normal rectal temperature. During the first, third and fifth of the periods separated by double vertical lines, while the subject was an outpatient, the time scale is contracted.

She was given penicillin at once and, on the suspicion that the rash might be toxic, thiourea was discontinued 4 days later. In the course of the next 9 days the temperature subsided, pains ceased, and the rash faded. On October 4, because SPI had risen from 6.6 to 11.3 γ per cent, thiourea was resumed in doses of 50 mg. daily. The temperature on 3 days rose to 100.6 to 100.8° but became and remained normal when the dose was raised to 75 mg.

After discharge, on November 1, through some error she took 210 mg. instead of 75 mg. of thiourea. By November 14 SPI had fallen, her skin was dry, there were no signs of rash, but she complained of vomiting and occasional chills and had tachycardia. Thiourea and Lugol's were discontinued on December 9. December 17 she had continuous aching in thighs and legs, chilly sensations, and a stiff neck. The muscles in the back of her neck were tender and her legs were tender and hot. She was admitted to the hospital with a temperature of 102.4°. Symptoms and signs subsided without specific treatment in a few days and remained in abeyance until her discharge on January 1, 1948, although she was given first 75 and then 125 mg. of thiourea. With the febrile episodes on both occasions she had a polymorphonuclear leucocytosis which reached a peak of 20,800.

Early in February she again developed pain and brawny swelling of one leg. Because SPI had risen to 11.3 γ per cent, thiourea was increased to 140 mg. By the end of another week the signs of inflammation in the leg had subsided. In April, when SPI had fallen to normal, she was given digitalis for exertional dyspnea and edema of the legs.

July 15 a maculopapular, erythematous, intensely pruritic rash appeared over her

arms and legs. When she was seen a week later, 150 mg. of propylthiouracil were immediately substituted for the 140 mg. of thiourea she had been receiving. The rash subsided within a few days. On August 17 the dose of propylthiouracil was reduced to 50 mg. daily. On this regime she has continued free from symptoms and working full time.

During her first and second admissions to the hospital her urine occasionally contained sugar. A fasting blood sugar on October 7, 1947, was 145 mg. per cent. Intravenous glucose tolerance tests on various occasions yielded the following results: October 8, 0 hrs. 161, 2 hrs. 162; October 20, 0 hrs. 95, 2 hrs. 83; December 18, 0 hrs. 99, 2 hrs. 119 mg. per cent.

In this case the relation of thiourea to rash, pains, and temperature was capricious. The reactions resembled those seen in the periodic infections of thrombophlebitic legs with lymphatic obstruction. On at least one occasion they disappeared without any change of the dose of thiourea and on two occasions persisted for considerable periods after thiourea had been discontinued. On the first admission thiourea was resumed, in small doses to be sure, only 72 hours after subsidence of the temperature, without untoward symptoms. The subsequent rash was of an entirely different character, more suggestive of an allergic reaction. Whether it should be attributed to thiourea it is impossible to say. In the face of the mere possibility that the drug might be responsible it seemed unjustifiable, so long as a substitute was available, to risk prolongation of the patient's distress.

A6280 (HM), female, born in 1878, reputedly had malaria in 1890, a dropsical condition of some kind in 1906, and in 1908 was told that she had heart trouble. In 1932 a radical mastectomy was performed for carcinoma of the left breast with metastases. At that time she also admitted nocturia 3 to 5 times a night. She was obese, her pulse 90, blood pressure 170/78. Physical and laboratory examinations revealed no other abnormalities. In 1943 she began to lose weight; in 1944 she noticed increasing nervousness and appetite, intolerance to heat, excessive perspiration and tremor. About July of 1945 dyspnea on exertion began; on October 3 she was seized with sudden palpitation and a choking sensation. On admission to the hospital next day she was breathless, with temperature 99.4°, pulse 100, respirations 32, blood pressure 200/70. The thyroid was enlarged and there was a fine tremor of the hands, but no exophthalmos. The heart was slightly enlarged, with a systolic murmur; the lungs were clear. The basal metabolism was +56 per cent, SPI 12.7 γ per cent. Her course is illustrated in Chart 6.

November 3 she was given intravenously 1 gm. of thiourea. November 5 she received 140 mg. and after that 210 mg. daily by mouth, without Lugol's solution. November 8 a slight urticarial rash appeared over the left forearm. It was learned that she had been subject to such rashes for many years. For the next few months the basal metabolism and SPI fluctuated considerably, although the dose of thiourea remained unchanged. For a time she lost a considerable proportion of her hair, suggesting myxedema,

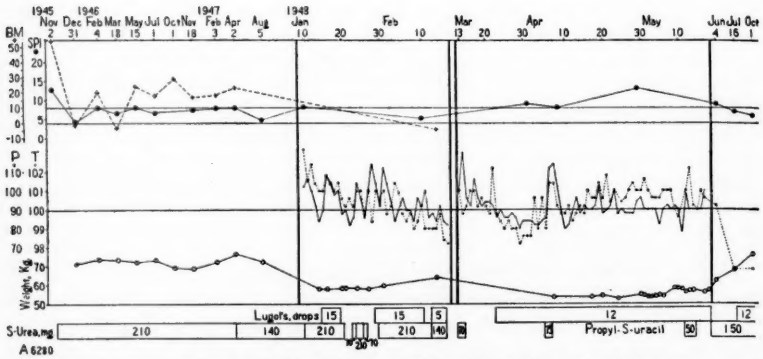
1945 1946 1947 1948
Nov Dec Feb Mar May Jul Oct Nov Feb Apr Aug Jan Feb Mar Apr May Jun Jul Oct
BM SPI
P T
Weight, Kg.
Lugol's, drops
S-Urea, mg
A 6280
Propyl-S-uracil

CHART 6. The two upper horizontal lines define the limits of variation of normal SPI, the lowest horizontal line the upper limit of normal rectal temperature. During the first, third and fifth of the periods separated by double vertical lines, while the subject was an outpatient, the time scale is contracted.

although both basal metabolism and SPI were within normal limits. In September, 1947, she noted weakness, anorexia, nervousness and sweating for a period, following a serious illness of her husband. By the middle of November she was forced to go to bed. A month later she reduced the thiourea to 140 mg. daily because of difficulty in swallowing solids, thirst, dyspnea, orthopnea, and palpitation.

January 9, 1948, she entered the hospital with temperature 102°, pulse 120 and irregular, and blood pressure 178/80, dulness at the left base of the lungs, with râles at both bases, venous pressure 50 mm., and circulation time 16 seconds. X-ray revealed pleural effusion and thickening at the left base with questionable infiltration of the left lower lobe; electrocardiogram showed a moderate left axis shift and multiple premature auricular beats. She was given digitalis. Blood culture, agglutinins, etc. were negative; the blood count was not remarkable; the urine was innocent except for slight glycosuria for a short period. The temperature fluctuated capriciously. January 20 it fell to normal while she was still taking 210 mg. of thiourea. It remained down for the next 3 days in which she received no thiourea or only 70 mg., rising again for 2 days when 210 mg. were given. It was again normal on January 26 when she took 70 mg., but rose to a peak of 102.4° on the 28th, the second day without thiourea. When thiourea and Lugol's solution were both resumed, the temperature gradually subsided again, but during this period she developed successively a transitory conjunctivitis and an erythematous rash on her thigh. February 13, since SPI had fallen to 5.4 γ per cent and the pulse was slow, the dose of thiourea was reduced to 140 mg. daily. She was discharged on February 24 with a normal temperature.

About February 29, while going to the bathroom, she fainted. About March 7 a rash appeared on her knees and elbows. She was readmitted to the hospital on March 13 with temperature 99.6°, pulse 84, blood pressure 110/60, drowsy, with thick speech, but oriented. Her face looked puffy and there were numerous hemorrhagic papular lesions about the knees, ankles, and elbows. Her heart was slightly enlarged and there were again signs of fluid at the left base. The temperature next day rose to 103°,

though she received only 70 mg. of thiourea, which was then discontinued entirely. Her chief complaints were weakness, dizziness, and pains on moving her legs. During the next 10 days the temperature fell and symptoms diminished. March 2 Lugol's solution was resumed. From March 23 to April 5 she was afebrile, but SPI rose from 5.4 to 9.2 γ per cent. March 7 and 8, when she was given 75 mg. of thiourea, the temperature rose to 102.2 and 102.4°, falling again in the course of the next 24 hours. At the same time an ulcer appeared on her gum. During the succeeding month, without thiourea, SPI rose to 13.2 γ per cent, the pulse became more rapid, she had irregular spikes of temperature to 101° and another ulcer appeared in the mouth. May 12 propylthiouracil in doses of 75 mg. daily was begun. The temperature rose on the 12th and 17th to 100.8 and 101° respectively, without symptoms. She was discharged on the 18th.

May 25, because of increasing exertional dyspnea and tachycardia and some edema of the legs, the digitalis was increased to 0.2 gm. daily. June 4, because of nervousness, clammy skin, and tremulousness, the dose of propylthiouracil was raised to 150 mg. daily. On this medication she has continued without further symptoms of importance and has regained an apparently euthyroid state.

In this case, on at least one occasion, there seems to have been a sharp febrile reaction to small doses of thiourea; but, with this exception, it is hard to establish a direct relation between the drug and fever or other symptoms. Discontinuation of thiourea for long periods on two occasions did not eliminate symptoms, although during her second admission these subsided while she was taking the drug. The nature of the recurrent pulmonary and pleural reaction was never definitely determined. It seems to have begun with a pneumonic process. Despite the signs of effusion, repeated thoracenteses yielded no fluid. She resembled the other patients who have been discussed in the rapidity with which SPI rose when thiourea was discontinued. Like them she did not appear to be unresponsive to the drug when it was resumed. When she became asymptomatic, her weight rose, while SPI and pulse fell, on a far smaller dose than that which had earlier been required to control her symptoms. Although it was not unequivocally proved, this must be regarded as a presumptive example of intoxication with thiourea.

B2143 (PC), female, born in 1920, was treated in 1940 for an indurative acne with local measures and injections of progesterone. In the summer of 1945, despite a ravenous appetite, she began to lose weight, became increasingly nervous and intolerant of heat, and developed tachycardia. Her thyroid enlarged and her menses became scanty. Her basal metabolism proved to be +30 per cent. Subtotal thyroidectomy was performed. After this she regained some weight, but irritability, nervousness, and hypermetabolism continued. A year later dyspnea on exertion was added. When seen on May 10, 1946, she had a palpable goiter, exophthalmos, a fine tremor, moist skin, a slightly enlarged heart with an apical systolic murmur, pulse 120, and blood pressure

140-150/80. Her basal metabolism was +39 per cent, SPI 8.1 γ per cent. Her course is illustrated in Chart 7.

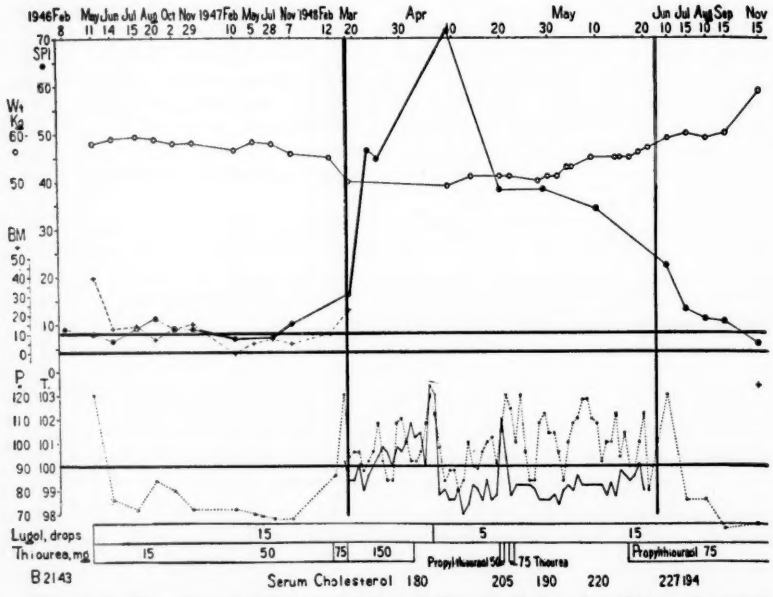
1946 Feb May Jun Jul Aug Oct Nov 1947 Feb May Jul Nov 1948 Feb Mar Apr May Jun Jul Aug Sep Nov
SPI
Wt Kg
BM
P T
Lugol, drops
Thiourea, mg
Propylthiouracil 50
75 Thiourea
Propylthiouracil 75
B 2143
Serum Cholesterol 180 205 190 220 227 194

CHART 7. The two upper horizontal lines define the limits of variation of normal SPI, the lowest horizontal line the upper limit of normal rectal temperature. During the first and third of the periods separated by double vertical lines, while the subject was an outpatient, the time scale is contracted.

On 15 drops of Lugol's solution and 15 mg. of thiourea daily, pulse and basal metabolism diminished; but SPI, after an early drop, rose again to hyperthyroid levels, where it remained. Her weight also failed to rise. In December the dose of thiourea was increased to 50 mg. Both basal metabolism and SPI fell to normal, but still her weight did not rise. May 31, 1947, tremor and sweating had ceased, but her palms were peeling which was attributed with some uncertainty to epidermophytosis. At the end of July she complained of watering eyes and orthostatic edema of the ankles without dyspnea. The urine was negative. Basal metabolism, SPI, and pulse were still normal. By November her weight had fallen further and SPI had risen to 9.8 γ per cent. In January, 1948, she began to suffer from pains, especially in the knees. In the middle of February a painful swelling of the left calf disabled her for 3 or 4 days. At the end of the month she had pains in her hands, elbows, and shoulders. Meanwhile SPI had risen and her weight had fallen further. March 12 canker sores appeared in her mouth.

March 19 she was admitted to the hospital in an emaciated state, with marked exophthalmos, acne of the face, pustules over the buttocks, a granulating ulceration in

the anal fold and small ulcers on the sides of her tongue, an enlarged heart with a rumbling systolic murmur at the apex, a presystolic murmur just to the left of the apex, and a friction rub just to the left of the lower part of the sternum. This last was noted on several subsequent occasions. Her lungs were clear. There was no edema. The liver seemed to be enlarged. Her temperature was 100.2°, pulse 120, blood pressure 120/66. Her skin was moist and satiny. Motions of the shoulders and elbows caused pain. The blood count was not extraordinary. Blood culture and antistreptolysin test were negative.

She was given aspirin and the dose of thiourea was increased to 150 mg. Nevertheless, and although she had received no organic iodine compound, SPI on March 23 proved to be 46.4 γ per cent and on the 25th was 44.8 γ per cent. Her weight had fallen further. The temperature touched 100° twice in the first 6 days, but when aspirin was discontinued on the 26th, it rose to 100.8 or 101°. March 26 she complained of substernal pain. This was one of the occasions when a pericardial friction rub was heard. Pains, mouth ulcers, and skin lesions continued to appear.

April 2 thiourea was discontinued. Four days later her temperature, which had been gradually mounting, rose sharply to 103.4°, to fall precipitately to normal 2 days later. At this time her cephalin flocculation test was 4+ after 48 hours, her metacarpophalangeal joints were painful, shoulders and knees ached, her right elbow was red and painful, her right wrist was swollen, and she developed subcutaneous nodules over the right elbow and about her knees. As the temperature subsided all symptoms and signs improved, but she had received aspirin during this period. April 13 she complained of pain in the right upper quadrant of the abdomen. The liver was found to be diffusely enlarged and tender.

April 19, when she had been afebrile for 11 days, she was given 50 mg. of propylthiouracil without obvious effect. The following day, after 70 mg. of thiourea, the temperature rose sharply to 102° and the next day the pains in the elbows and shoulders became exaggerated. The febrile reaction persisted only 48 hours. In the following 3 days new skin lesions appeared on her face, lip, and buttock, and a fresh nodule on her finger. From that time through May 19 she continued to have recrudescences of joint pains and new oral lesions and subcutaneous nodules. Beginning on May 16 propylthiouracil was given in increasing doses up to a daily dose of 75 mg. on the 18th, without especial untoward symptoms. A new lesion did appear on her tongue on the 19th. During her course in the hospital she had a polymorphonuclear leucocytosis that on one occasion was as high as 14,500.

June 11 she still had some pains in her knees with slight effusion in the right, as well as a small ulcer on the border of her tongue. July 15 her knees still ached, and ulcers continued to appear in her mouth. August 10 symptoms had almost disappeared, but on the 16th she had an ulcer on her third left toe, on the 23d nodules on the tips of two fingers. These all disappeared fairly rapidly. When seen September 14 a new nodule had appeared on her thumb, had opened, discharged, and healed. On the 20th she had a crop of acneiform pustules on her arms and legs as well as on her face, which resembled the lesions that had previously been termed nodules. At this time Lugol's solution was stopped, but November 15 the acne was unimproved. She appeared euthyroid. Except for the acne she has been free from symptoms since that time.

The course of the SPI in this case is altogether unique. Attention has already been called to the extraordinary rise that accompanied the rheumatic disorder, without any

change of therapy. Because of the high SPI the dose of thiourea was first doubled to 150 mg. per day for 12 days. The drug was then discontinued for reasons mentioned above. At the end of 5 days SPI was found to have risen to the unprecedented figure of 71.5 γ per cent. Thereafter, without medication, it gradually receded as fever and other symptoms subsided, to reach 34.4 γ per cent by May 10. A month after propylthiouracil was given it had fallen further to 22.2 γ per cent. At this time the patient still had symptoms and signs of hyperthyroidism, but seemed otherwise well. With further improvement and disappearance of evidence of excessive thyroid activity, SPI ultimately, on November 15, had fallen to 6.0 γ per cent, an entirely normal value.

This case is distinguished from the others in that the patient was a young adult without evidences of antecedent vascular disease. The initial elevation of systolic blood pressure must be discounted, since the pressure was subsequently consistently normal. Furthermore, the symptoms began after small doses of thiourea. As in the previous case, on one occasion a comparatively small dose of thiourea appeared to precipitate a striking febrile reaction with exacerbation of symptoms. Similar symptomatic exacerbations without fever occurred, however, at intervals throughout a period of weeks during which she received no thiourea. The clinical pattern and course of the disease were indistinguishable from that of rheumatic fever or one of the allied disorders. The evidence that the symptoms in this case were referable to thiourea is less convincing than it was in the two preceding cases. They subsided only long after propylthiouracil had been substituted, and then only stepwise. The arthritis outlasted the temperature by a considerable interval. The lesions of the mouth continued still longer. It is hard to say when the skin lesions ceased because of the confusing presence of an acne of unusual distribution. This, it will be recalled, had been noted and treated in 1940 when the patient also complained of pains in her neck and chest.

Five patients died while receiving thiourea or propylthiouracil. Autopsies were obtained on all.

C6107 (MW), female, born in 1893, had a thyroidectomy for hypertension in 1919, after preliminary treatment with radium. Gradual recurrence of symptoms in 1930 led to a second operation in 1934 that gave conspicuous relief, though it left residual fatiguability, weakness, and palpitation. In 1945 she was given injections by her physician for hot flashes, although her menses had not ceased. About this time her goiter reappeared, accompanied by increased palpitation and fatigue, with tremor, sweating, shortness of breath, and loss of weight. Her menses gradually ceased in 1947. In the fall of that year, following a cold, she developed a persistent cough. About 1945 she began to have nocturia 2 or 3 times a night. No history of rheumatism could be elicited.

When seen, January 8, 1948, she was wasted (her weight had fallen from 145 to 105 pounds), tremulous and restless, with moderate exophthalmos, temperature 101°,

pulse 120 and totally irregular, blood pressure 180/75. She had a large goiter, involving especially the left lobe of the thyroid. The heart was grossly enlarged and fibrillating, râles were heard at the bases of both lungs and in the right axilla, the liver was down 2 fingerbreadths, the spleen 2 to 3 fingerbreadths. X-ray revealed enlargement of the left auricle and ventricle and minimal pulmonary congestion. The basal metabolism was +87 per cent, the serum precipitable iodine 30.2 γ per cent. She was immediately digitalized and given 15 drops of Lugol's solution and 210 mg. of thiourea daily. By January 21 the SPI had fallen to 14.2 γ per cent, the pulse to 96, sweating and tachycardia had diminished. February 25 improvement had continued. SPI was 8.1 γ per cent, though the basal metabolism was still +54 per cent and her weight had not risen.

At this time her daughter had mumps and the patient was found to have non-tender enlargement of the right submaxillary gland. Two days later she developed pains in the legs, later spreading to the arms, with red and swollen joints. These improved for a week, when she developed a "pneumonic condition" for which she was given injections of penicillin 4 times a day for 2 weeks. Again her condition improved; but on March 14 her fever rose sharply, she became delirious, unable to take food, extremely nervous and sleepless, and incontinent of urine and feces. Lugol's solution had been discontinued March 4, thiourea, March 13. Digitalis had been continued.

When admitted to the hospital, March 18, she was delirious and so hyperactive that examination was impossible. Her temperature was 102°, pulse 124. Twelve hundred cc. of normal urine were withdrawn by catheter from a distended bladder. The next morning her temperature was only 100.2°, pulse 132 to 100, respirations 30, blood pressure 140/60. She was emaciated, feeble, trembling all over. She had marked exophthalmos with conjunctival injection. The precordium was heaving, the heart totally irregular with tumultuous sounds, a systolic thrill and murmur. The bladder was again distended. The left knee was painful and swollen. In the afternoon she suddenly went into a state of collapse, with cold clammy feet and hands, fine and coarse râles all over both chests, pulse 160, and blood pressure 140/90. She died before anything could be done. The leucocyte count was normal, but she had a slight secondary anemia. The serum precipitable iodine was not determined during her terminal illness.

Anatomical findings at autopsy: Hyperplastic thyroid remnant (105 grams); segmental necrosis of coronary, renal, adrenal, splenic, and pancreatic arteries; hypertrophy and dilatation of the heart; confluent focal pneumonia (mixed infection).

Subsidiary findings: An occasional lesion in the liver, lungs, and lymph-nodes suggesting Boeck's sarcoid; minimal cortical gliosis.

Microscopically the thyroid was made up of hyperplastic and atrophic follicles with increased interstitial lymphoid and connective tissue.

There was practically no arteriosclerosis of the aorta or of the great arterial trunks. Striking mural changes were present in the small muscular arteries of the heart, kidneys, adrenals, spleen, and pancreas. Fibrinoid necrosis of the media was prominent. An inflammatory cellular exudate accompanied this medial necrosis, forming accumulations of leucocytes within or around the vessel wall. No eosinophiles were found. Occasionally elevation of the endothelium had occurred but no thrombi were observed. Occasional sites of fresh collagen replacement were present in the media, but other than this there was no evidence of proliferation or healing in the vessels. The lesions

were all approximately equal in age. Nearly every interlobular artery in the kidneys and nearly all the smaller arteries of the pancreas were involved. In the other organs, somewhat fewer arterial changes were present.

There was no evidence of old or recent rheumatic carditis. The sarcoids observed were small and apparently in the healing stage. The salivary glands were not examined. The focal pneumonitis was fresh and widespread in the lower lobes.

The autopsy findings in this case are peculiarly at variance with the clinical course. For the last 30 years of her life the patient had suffered from recurrent hyperthyroidism. In the last 3 years symptoms of cardiac embarrassment appeared. In the fall of 1947, 3 or 4 months before death, following a respiratory infection, these became worse. When seen in January she presented the picture of extreme hyperthyroidism and congestive failure with an extraordinarily high SPI. Her response to thiourea and iodine was prompt and highly satisfactory until the onset of her final illness. This again may have been an infection, characterized by pneumonia and arthritis, which subsided after penicillin. With a recrudescence 2 weeks later she went into a state that, had she not received thiourea, might well have been termed a fatal "thyroid storm." So desperately ill was she and so brief was her course in the hospital that there was no time for diagnostic nor therapeutic measures. Except for the progressive increase in severity and the appearance in the last illness of arthritis there is nothing to distinguish the reaction of the patient to her various infections. At autopsy there was a confluent pneumonia and a widespread acute vascular reaction, but no adequate explanation for the earlier cardiovascular symptoms which were unmistakable and preceded the administration of thiourea. Although the drug may have contributed to the denouement, this background can not be neglected; nor can the possibility be excluded that infection rather than thiourea was responsible for the illness as well as its fatal outcome.

B7801 (GB), female, born in 1885, was married in 1905 and gave birth to an only son the following year. In 1925 she went into an acute depression following an operation for retroversion of the uterus. Early in the spring of 1940 she became more tense and nervous than usual. In August she was admitted to the Psychiatric Ward in a state of extreme agitation and depression and bromidism. She was discharged, improved, after a month. In August of 1941 she was again admitted in a similar state. This time she remained in the hospital for 2 months. March 1, 1945, she was admitted for the third time. On all these occasions her pulse in the hospital had been abnormally rapid, tremors and motor activity had been noted, and her blood pressure had been variably elevated. On each occasion the temperature was elevated at the outset. During this 1945 admission, the SPI on March 6 was found to be 12.6 γ per cent. Lugol's solution was given at once. Her course is illustrated in Chart 8. By March 19, after

13 days of medication, tachycardia and other symptoms had disappeared and the serum precipitable iodine had become normal. For some reason, medication was discontinued after her discharge.

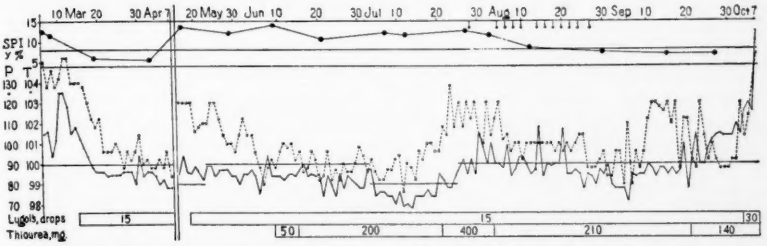

CHART 8. The two upper horizontal lines define the limits of variation of normal SPI, the lowest horizontal line the upper limit of normal rectal temperature which is assumed to be 100° by rectum, 99° by mouth. The shifting position of this line during the second day in the hospital indicates that the temperature was taken for some periods by mouth and for others by rectum. The vertical arrows at the top of the figure indicate electric shocks.

Beginning May 2 she became increasingly disturbed until her readmission on May 16, when her pulse was 120, her blood pressure 180/80, and she was in an unmanageable state. Her serum precipitable iodine was 13.6 γ per cent. Lugol's solution was resumed. By June 9, though the pulse rate had fallen somewhat, the SPI was still 13.8 γ per cent and there had been little clinical improvement. Thiourea was, therefore, given, 50 mg. daily at first, increased to 200 mg. after a week. July 25 the psychotic state was unrelieved. An elevated temperature was noted at this time (it had probably preceded this, but had not been recognized because oral temperatures had been taken). July 28 some edema of the ankles was noted, although she seemed dehydrated. It was impossible from this time on to evaluate her physical condition owing to her mental state. The thiourea was increased to 420 mg. from July 21 to 31 because of the striking tachycardia and high SPI. At the end of this time the previous dose was resumed. Two weeks later the serum precipitable iodine had fallen to 8.2 γ per cent; subsequently it descended to 7.0 γ per cent. Fever, tachycardia, and edema, however, persisted. Before this time tube feeding had been instituted, as a result of which her throat became quite sore. She had also been subjected to electric shocks during the period of high thiourea dosage. She deteriorated steadily until her death on October 7, which was preceded by a short period of steadily rising fever. She had a variable leucocytosis towards the end of her course.

Anatomical findings at autopsy: Nodular hyperplasia of thyroid (60 grams); generalized arteriosclerosis and arteriolosclerosis; coronary arteriosclerosis; cardiac hypertrophy and dilatation; scars of myocardium; thrombi in pulmonary vessels; infarcts of lungs.

Subsidiary findings: Pulmonary emphysema; chronic gastritis; leiomyomas of uterus.

The thyroid follicles were composed chiefly of dilated acini containing much colloid, suggesting iodine effect. Several areas of hyperplastic epithelium were present as well.

Sclerosis of the aorta was severe. In the arch a small mural thrombus was present. The underlying intima was not only fibrous and thickened but was edematous and contained a diffuse cellular exudate of lymphocytes, polymorphonuclear leucocytes, and plasma cells. Sclerosis of the visceral arterioles was also severe. It was of the subendothelial hyaline variety, without evidence of any acute process. The interlobular vessels of the kidney and the larger renal vessels were particularly involved, as were the peri-adrenal and pancreatic arterioles. The kidneys were not scarred, weighing together 325 grams. The coronary vessels were calcified but patent. There was lipomatosis of the myocardium besides the focal scarring. The mitral valve leaflets were thickened, with fused chordae tendineae. Beyond this there was no suggestion of old or recent rheumatic carditis. The pulmonary infarcts were recent.

In this case arterial disease had obviously preceded the final illness and administration of thiourea, although little clinical evidence of such a condition had been found. The mental state of the patient prevented a satisfactory clinical analysis. It is quite uncertain whether fever followed or preceded administration of thiourea.

B54264 (ER), female, born in 1903, was seen in the prenatal clinic May 1, 1944, in the 7th month of her 6th pregnancy, with blood pressure 140/90, urine negative. Between this time and her delivery on July 30 her weight rose from 152 to 176 lbs., with the appearance of some edema of the ankles, but no further hypertension. One blood pressure in the hospital was 150/90. A catheterized urine was normal. Her thyroid at that time was reported not enlarged.

May 31, 1945, she was admitted to the hospital, complaining of swelling of the neck, loss of weight, extreme nervousness, occasional difficulty in breathing, and orthostatic swelling of the ankles. She had a staring expression, fine tremor of the hands, a diffusely enlarged thyroid, moist skin, lenticular opacities, pulse 120, blood pressure 140/60. Her basal metabolism was +55 per cent, SPI 14.3 γ per cent. Blood count and urine were normal. Her course is illustrated in Chart 9. By June 14 on rest alone the basal metabolism had fallen to +48 per cent, the SPI to 9.0 γ per cent. She was given 15 drops of Lugol's solution and 200 mg. of thiourea daily. By the end of July, much improved, her basal metabolism was +21 per cent, SPI 5.1 γ per cent. Shortly after this, for no obvious reason and without change of treatment, pulse, basal metabolism, and serum precipitable iodine rose for a short period to hyperthyroid values. This hyperthyroid phase was preceded by a short hypothyroid episode.

April 9, 1946, she was admitted to the hospital for a cataract operation, with slight tachycardia, but normal temperature. The day after operation her temperature rose to 101°. From that day until her discharge on April 23 she had a low grade intermittent fever, apparently associated with a laryngitis. The SPI the day before her discharge was 7.1 γ per cent. Between that date and December 20 it rose steadily to reach the extraordinary figure of 46.0 γ per cent.

Some time between June and August she began to suffer from pains in her joints, without swelling or redness. She subsequently stated that these cleared up when she stopped thiourea, recurring when she resumed the drug. She also said that her nervousness returned when she discontinued the drug. Presumably, then, the treatment was intermittent during this period, but there is no record of the interruptions. November

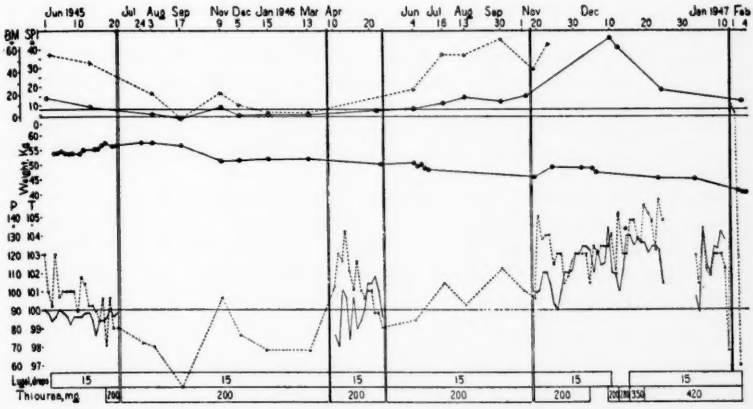

CHART 9. The two upper horizontal lines define the limits of variation of normal SPI, the lowest horizontal line the upper limit of normal rectal temperature. During the second, fourth and sixth of the periods separated by double vertical lines, while the subject was an outpatient, the time scale is contracted.

12 an ulcer appeared over her left internal malleolus after an accidental kick. She was admitted to the hospital November 19, with temperature 100.8°, pulse 120, blood pressure 142/84, hyperactive, with characteristic moist skin, slight exophthalmos, an enlarged thyroid gland, a faint blowing aortic systolic murmur without signs of heart failure, and sluggish ulcers over the left internal malleolus. The temperature rose steadily to reach 103.4° on December 2, without further signs or symptoms, despite a course of penicillin. Thiourea was discontinued for 5 days, beginning December 3, but the temperature remained elevated and on the 8th she developed an ulcer on the bridge of her nose, at the point of contact with the nosepiece of her spectacles. Blood cultures and agglutination tests were all negative.

At this time, because of the high serum precipitable iodine and basal metabolism, and extreme tachycardia, thiourea was resumed in doses that were increased to 420 mg. daily. Temperature and tachycardia persisted. She was discharged against advice on December 24, at which time she complained of hoarseness. The urine had been consistently negative. There had been a leucocytosis up to 13,500, with a normal differential count.

She was readmitted to the hospital January 2, 1947, for 9 days, subjectively improved, but still hoarse, with some nasal discharge, temperature 100.2°, pulse 112, blood pressure 106/70. The ulcers on her ankle were almost healed, but the lesions on her nose persisted. Her liver was slightly enlarged. X-rays of the chest and abdomen were again negative, blood counts and urines normal. The temperature again rose almost daily to 103 or 104°. Although the serum precipitable iodine had declined, it was still definitely above the normal range. She was seen again on February 2, 3, and 4, desperately weak and shaky, with a tachycardia of paroxysmal proportions on the

first 2 occasions. She died at home on April 30. The white blood cell count was normal except for a short leucocytosis up to 16 to 18,000 early in December 1946.

Anatomical findings at autopsy: Emaciation, diffuse enlargement and hyperplasia of thyroid; ulcers of skin of extremities and nose; focal acute and organizing pneumonia, lower lobes.

The thyroid gland weighed 45 grams and microscopically was composed throughout of small acini with hyperplastic epithelium and little colloid. There was no anatomical evidence of iodine effect.

Minimal aortic arteriosclerosis was present. No other lesions of arteries or veins were found. Microscopically the ulcers of the skin revealed a superficial non-specific chronic inflammatory process, without particular involvement of the regional vessels.

The heart weighed 225 grams and was not remarkable. There was no evidence of hyperplasia of the parathyroids.

In this case autopsy disclosed no explanation for the extraordinary cardiovascular disorders from which the patient had suffered and which had been such a prominent feature of her final illness. The skin lesions, which were nondescript in character, may have represented a reaction to thiourea. The record, however, again indicates that an acute disorder, accompanied by joint pains, and suggestive of an infection, precipitated an uncontrollable outburst of hyperthyroidism. Unfortunately there is no record of her course during the last 3 months of life.

B99489 (AP), female, born in 1896, was seen in the dispensary July 8, 1947. For 2 or 3 years she had been nervous and had experienced difficulty in maintaining her weight, despite a good appetite. She had been given "nerve capsules" for hypertension. In April or May, 1947, the nervousness increased, accompanied by tremor, tachycardia, palpitation, breathlessness, and pruritus. She appeared well nourished, though she had lost 30 pounds, extremely hyperactive, with a marked tremor, hot moist skin, a slightly staring expression, slight enlargement of the thyroid and the heart, a widely disseminated systolic murmur, but clear lungs, pulse 134, blood pressure 190/84. The basal metabolism was +41 per cent, the SPI 14.1 γ per cent. She was at once given 10 drops of Lugol's solution and 225 mg. of propylthiouracil daily. Her course is illustrated in Chart 10.

By August 8 the basal metabolism had fallen to +2 per cent, the serum precipitable iodine to 7.5 γ per cent, the pulse was in the 90's, and her weight had increased 3 kg. She complained only of pain in her back and left hip which dated from an accident in 1940. X-ray revealed a narrowed interspace between the 5th lumbar and 1st sacral vertebrae and an anomalous transverse process on the former. At this time the propylthiouracil was reduced to 150 mg. daily.

August 22 she complained of some residual nervousness, tremor, and fatiguability. September 3 she complained of a slight cold. Her pulse was 90. From this time until January 30, 1948, her SPI rose steadily to 14.0 γ per cent, her pulse became more variable and she complained of increasing nervousness, although her weight rose slowly. The basal metabolism lagged far behind the serum precipitable iodine and signs of hyperthyroidism were not striking. On March 19, the serum precipitable iodine

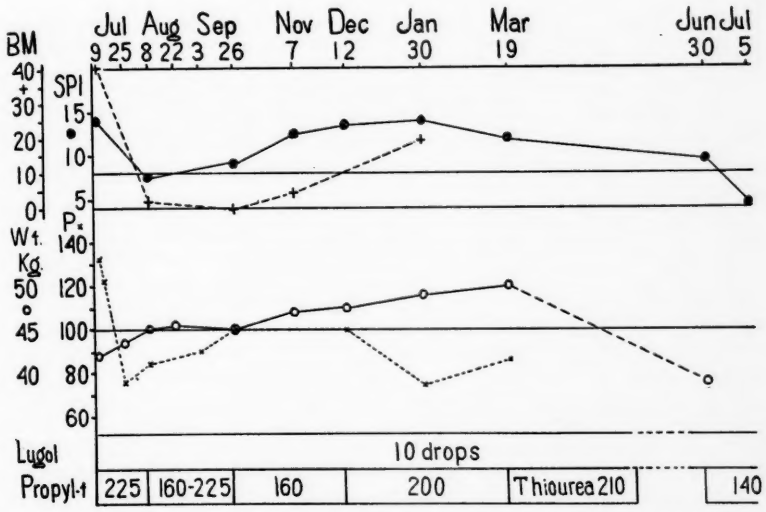

CHART 10. The two upper lines define the limits of variation of normal SPI. The time scale is not precise; it is only intended to show the state of the patient on the days on which she was seen.

being 12.2 γ per cent, 210 mg. of thiourea daily were substituted for propylthiouracil.

Some time in May she had hives for a few days, followed by an acute illness characterized by sore throat, fever, severe general aches, prostration, and delirium. A diagnosis of pneumonia was made by her family physician, who gave her both sulfadiazine and penicillin. At the same time diabetes was discovered (there is no previous record of a urine examination) and insulin therapy was begun, while Lugol's solution and thiourea were discontinued. Lugol's solution was resumed on June 14 and thiourea on June 30. On June 14 she reported deterioration of vision. Her pulse was 94, blood pressure 158/110, there were hemorrhages in both macular areas, the urine gave a 1+ reaction for albumin, none for sugar (she was receiving 20 U. of insulin per day), and contained a few white blood cells.

She apparently remained fairly well until July 13, when she had a severe insulin reaction in which she became maniacal. The insulin was reduced to 10 U. of protamine on July 14. That day she developed fever, generalized pains, and malaise. The next day she was again given 10 U. of protamine insulin and thiourea was omitted. The following day, July 16, she was brought to the Emergency Ward of the hospital, having received no insulin, flushed, disoriented, and combative, with temperature 102°, pulse 184, respirations 38, and blood pressure 205/105. She complained of great hunger and thirst, took her dinner and drank ice water without vomiting. Her skin was hot and dry, her neck somewhat stiff; she had moderate exophthalmos, an extremely hyperactive heart and some râles at the base of the right lung.

Through failure to recognize the precise nature of her condition and consequent

errors of therapy, she died in a state of shock the next morning. Discussion of the details of this unfortunate episode are irrelevant and would divert attention from the immediate subject.

During the earlier phase of her last illness she is reported to have had a severe anemia. When admitted to the New Haven Hospital her red blood cell count was 8.6 million, hemoglobin 13.5 gm., white blood cells 48.2, with 30 per cent non-segmented and 60 per cent segmented forms. Obviously she was in a state of extreme hemoconcentration.

Anatomic findings at autopsy: Hyperplasia of the thyroid gland with areas of marked involution; pancreatic fibrosis; widespread segmental necrosis of small arteries in the thyroid, liver, gall bladder, spleen, omentum, bone marrow, and salivary glands; pulmonary congestion and edema. There was moderate intimal arteriosclerosis of the aorta and larger vessels, and a chronically inflamed Meckel's diverticulum.

The thyroid gland weighed 37 grams. It was nodular grossly. Microscopically, connective tissue and lymphocytes were increased between groups of dilated acini. Many of the acini were filled with homogeneous, eosinophilic colloid. Occasional groups of small acini with high cuboidal epithelium and without colloid were present, suggesting hyperplasia.

Changes in the small arteries throughout the viscera consisted of segmental medial necrosis accompanied by cellular exudate involving in varying degree the three arterial coats. The cellular exudate was composed of mononuclear cells and a few polymorphonuclear leucocytes. Accumulations of these cells were often present microscopically in the periadventitial tissues. No eosinophils were found, although subendothelial accumulations of exudate were observed. No thrombus formation had occurred. The changes in the arteries described were all approximately in the same acute stage, except those in the pancreas.

The sublingual and submaxillary glands were the seat of a diffuse acute interstitial inflammation, which appeared to be an extension of the necrotizing process in the arterioles.

Interstitial fibrosis of the pancreas was widespread with reduction of acinar and islet tissue. Accumulations of lymphocytes and polymorphonuclear cells were scattered throughout the gland. While necrosis of the pancreatic arterioles was not found, several showed fibrous replacement of their media with periadventitial fibrosis.

No evidence of rheumatic carditis was present. Intercapillary glomerulosclerosis was not found in the kidneys.

Death in this case can be attributed directly to shock from diabetic acidosis. The diabetes either arose or became apparent during an illness that first manifested itself in urticaria, shortly followed by a condition which was interpreted by her physician as infectious in origin. This began almost a year after the institution of treatment of hyperthyroidism with propylthiouracil and 2 months after thiourea in large doses had been substituted. That this was associated with acute arterial disease which persisted for the better part of a month after the drug was omitted can be inferred from the hypertension and fresh retinal lesions observed on June 14. Although the nature of this illness suggests, and the character of the vascular lesions

found at autopsy is compatible with, reaction to a drug, the final outburst did not occur until 2 weeks after she resumed thiourea. Granted that this was thiourea intoxication, the origin of all her major troubles appears to have been an exacerbation of her hyperthyroidism by a respiratory infection early in September of the preceding year.

C11918 (ES), female, born in 1894, was mentally deficient. Of her 4 children, 2 also proved to be defective. In 1929 she was admitted to an institution and in 1930 was sterilized. In 1937 bilateral pulmonary tuberculosis was discovered by x-ray. From 1940 to 1942 the lesions seemed to advance somewhat; but thereafter appeared to be quiescent. At this time she was admitted to the Southbury Training School, where attention was drawn to a goiter which was said to have been present since 1907.

In 1947 increased nervousness and hyperactivity were noted, together with tremor of the hands and tachycardia. The basal metabolism proved to be +62 per cent. She was given 15 drops of Lugol's solution and 75 mg. of thiourea daily. Her course is illustrated in Chart 11. In February, 1948, and again in April, because the basal metabolism remained elevated, the dosage was increased successively to 150 and then to 200 mg. May 25 the basal metabolism was still +69 per cent and nervousness and tachycardia persisted despite restricted activity and partial bed rest. There is some doubt, however, whether the patient took her medicine regularly.

Because of her unreliability and failure to respond to therapy, she was sent to the New Haven Hospital for thyroidectomy on June 2. On admission the temperature was 98.8°, pulse 146, respirations 26, blood pressure 110/70. She was thin, hyperactive and silly, with excessively moist skin, bilateral enlargement of the thyroid, slight lid lag, slight dulness over the apices of both lungs, and a slightly enlarged heart with tic-tac sounds. The antithyroid therapy was continued unchanged. June 9 the temperature rose and June 13 urinary frequency was noted. Hemolytic streptococci were recovered from the catheterized urine. It was discovered that the patient belonged to that class of women who seem unaware of a full bladder when they are in the recumbent position. June 15 she was given penicillin which brought the temperature to normal after 8 days.

June 26, because the SPI and pulse were still elevated and the weight was falling, the dose of thiourea was increased to 280 mg. daily. July 4 the temperature again began to rise. An infected tooth was extracted on July 9, but the temperature continued to rise in spite of penicillin. July 11 a heavy growth of E. coli was recovered from the urine. She was given full doses of sulfadiazine without apparent effect, but it was discovered that she had been hiding the pills. She had meanwhile lost much weight, her appetite had deteriorated to such an extent that she required parenteral fluids, and intermittent glycosuria had appeared. Blood sugars, at first equivocal, later became consistently elevated.

On July 27 her neck and upper anterior chest assumed a deep purplish-red hue, which blanched on pressure, her pulse rose to 186 and her respirations to 55, without orthopnea. A moderate secondary anemia had not been greatly affected by a transfusion. The temperature persisted and E. coli continued in the urine. Probably because of the high doses of thiourea the SPI had fallen to 6.5 γ per cent. Emaciation and weakness increased continuously. July 30 she complained of photophobia, her neck

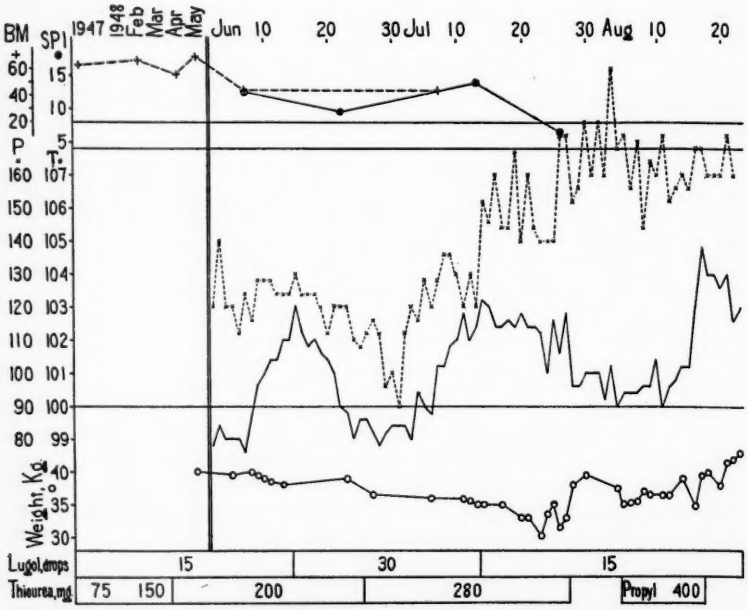

CHART 11. The two upper horizontal lines define the limits of variation of normal SPI, the lowest horizontal line the upper limit of normal rectal temperature. During the first of the two periods separated by the vertical double line, before the patient entered the hospital, the time scale is contracted.

was stiff, reflexes absent, and a small hemorrhage was seen in the left retina. Profuse râles were heard over the bases of both lungs, especially the left, and the liver seemed to be enlarged. The catheterized urine was loaded with white blood cells and organisms. Meanwhile streptomycin and digitalis had been begun. By August 2 her circulatory state seemed improved; but 2 days later cyanosis and extreme tachycardia recurred. More scattered retinal hemorrhages and blurring of the optic discs were found. The spinal fluid was normal except for slightly increased pressure. Edema, which had appeared somewhat earlier, increased. Urine cultures continued to defy therapy.

August 6, propylthiouracil, 400 mg. daily, was started because of the extreme persistent tachycardia. By this time she was practically unable to move her lower extremities, and her arms were so weak that she could not feed nor help herself, though she took nourishing fluids when they were given to her. There was diffuse tenderness in the lower extremities. On August 15, 11 days after propylthiouracil was begun, her temperature, which had for a long time varied between 100.4 and 101.2°, rose to 103°. From this time until her death, 8 days later, it ranged between 102.6 and 104.8° daily, although propylthiouracil was stopped on the 17th. Penicillin had been given in doses of 600,000 units daily for a long time before this. With this terminal

temperature, signs of pneumonia appeared in the left lower lobe, later spreading to other parts of her lungs. In the latter part of her course, x-ray revealed enlargement of the heart, a right pleural effusion, and pulmonary congestion. During the terminal episode, because of her desperate condition, no x-rays were taken. On admission to the hospital she had a leucocytosis of 13,800, toward the end this had risen to 28,400, with 20 per cent non-segmented and 72 per cent segmented forms. She also had a secondary anemia.

Anatomical findings at autopsy: Adenomatous goiter (165 grams); bilateral old fibro-caseous and calcific pulmonary tuberculosis; confluent tuberculous pneumonia; generalized arteriosclerosis; obliterative endarteritis of arteries of the kidneys and periadrenal fat; scars of kidney cortex; infarct in left kidney; infarcts of spleen; organizing thrombus in left ovarian and renal vein; atrophy of cerebral cortex; symmetrical dilatation of cerebral ventricles.

The thyroid acini microscopically revealed involutional changes characteristic of iodine effect. Groups of hyperplastic acini were interspersed among the involved follicles.

The arterial lesions of the kidneys consisted of an old obliterative intimal and medial process involving segments of the interlobular vessels. Identical changes were found in the pericapsular arteries of the adrenals. Although scars were present in the renal cortex the microscopic appearance of the kidneys was not that of ordinary pyelonephritis. In some situations the vessel changes were present in relation to scarred areas of cortex, but more often they were not. Furthermore the arterial lesions were definitely out of proportion to the other changes present in the renal parenchyma. An infarct was present in the left kidney, the renal vein of which was occluded by an organizing thrombus. The splenic arterioles were the seat of hyalin arteriosclerosis. No old or recent occlusions of these were demonstrated to account for the recent infarcts. No acute arteriolar changes were present in any of the viscera.

There was moderate dilation and hypertrophy of the right ventricle. The liver showed severe chronic passive congestion. There were no anatomical lesions of the pancreas to suggest diabetes, nor were intercapillary changes present in the glomeruli of the kidneys.

This patient has been included in the series because the clinical course of her disease does not differ greatly from that of some of the other cases that have been described. She can be distinguished from them only by the fact that autopsy revealed reasons enough for symptoms and death without implicating thio-drugs. Death may be attributed to her tuberculosis. The arterial disease, though somewhat atypical, may be ascribed to the pyelonephritis. Unexplained thrombophlebitis is so commonly encountered in chronic diseases that no specific importance can be attached to it. She illustrates resistance to the action of thiourea—or more precisely, perhaps, exaggeration of hyperthyroidism—in the presence of infection. It was, however, possible by large enough doses of thio-drugs to bring the hyperthyroidism under control.

Discussion

Although this paper deals chiefly with the effects of thiourea, the phenomena which it describes have been observed in varying degree after all thio-drugs. Thiourea is given prominence in this particuar series only because, for reasons stated above, it was, until recently, employed more than any other member of its group.

The vomiting and febrile reactions occurring early in the course of treatment with thio-drugs are unmistakably connected with these drugs. These febrile reactions, like the occasional urticarial incidents, appear to be allergic in nature. They are among the trivial allergic reactions that can be elicited acutely by administration of the drug and are rapidly self-terminative. It has been claimed, and in many instances demonstrated, that they cease spontaneously after a short time if administration of the drug which provoked them is continued. Since they are usually quite specific, it is more advisable to substitute for the offending drug some other member of the thio-group. Pathological leucopenia and agranulocytosis can also be referred directly to the action of the drug, although it is more than possible that other concomitant medications may have been responsible for some of the cases that have been reported. In this respect thiourea has a peculiarly innocent record.

It is far more difficult to establish a direct connection between the thio-drugs and the late febrile disorders with which the body of this paper is concerned. Even the autopsy findings in the 5 fatal cases are inconclusive. Although these complications began while the patients were receiving thiourea, definite association between the drug and fever or other symptoms could not be demonstrated. Febrile responses and other symptoms were clearly provoked by administration of thiourea in only 2 cases, A6280 and B2143; and in the latter on other occasions temperature and skin lesions appeared after the drug had been withdrawn and disappeared while it was being given. It is this uncertainty which has compelled us to report all the cases in detail.

One obstacle to the analysis of the problem is our relative ignorance of the life history of patients with hyperthyroidism—what happens to them with respect to other functions than that of the thyroid gland or beyond that brief span or those recurrent episodes in which they interest the surgeon or the endocrinologist. Selvaag[40] in a series of 392 patients with hyperthyroidism found 9 with polyarthritis, 9 with humeroscapular arthritis, and 2 with rheumatic fever, a proportion that compares well with that seen in the present series of treated cases. It would be unjustifiable to exonerate

thio-drugs on the basis of this evidence; but it serves to emphasize the need for a broader study of hyperthyroidism and its associations.

It is necessary also to inquire whether the patients that have been described belong to a particular class possessing pre-existing characteristics that render them peculiarly susceptible to the types of reactions that have been described. They are certainly not representative of the usual composition of a thyroid clinic. Of the 12 only 1, B2143, was under 30 years of age, 1 was under 50, 5 were more than 60 years old. Four had persistent outspoken hypertension; 4 others had high blood pressure at some time in the course of their illnesses. Four had frank congestive heart failure when treatment was begun and 3 others required digitalis at some time. Measurement of SPI has facilitated the diagnosis of hyperthyroidism in patients with heart failure. This and the fact that patients with circulatory complications are particularly likely to be referred for medical treatment has given this clinic a somewhat unusual complexion. Nevertheless, it is a matter of surprise that the younger population of the clinic has so generally escaped these possibly toxic complications.

Of the 12 patients suspected of late febrile reactions, all but 2 had received large doses of thiourea, 200 mg. or more, usually for long periods. With the exceptions of C6107 and B7801, the duration of treatment varied from 10 to 22 months. These large doses were required in these cases to control hyperthyroidism. In some instances attempts to reduce the quantities of thiourea led to recrudescence of thyrotoxic symptoms; in some, such symptoms could be controlled by small doses. Others, because of some intercurrent condition, the nature of which was not always clear, developed evidences of hyperthyroidism while on moderate doses that had been adequate, necessitating the use of larger doses. These febrile complications, therefore, appeared most frequently in subjects who were resistant to the action of the drug. This resistance or variability in the response to therapy is common to all thio-drugs. The doses required for the control of hyperthyroidism are not proportional to the severity of the clinical manifestations nor to the degree of disturbance of the objective criteria of activity, basal metabolism and SPI. In the course of treatment, moreover, on a constant dose, evidences of activity vary widely in a certain proportion of cases. It is conceivable that the febrile episodes in these cases are directly referable not to the large doses of drug that were given, but to the factors that created the resistance that made these large doses necessary.

In almost every instance these late febrile reactions were preceded or accompanied by signs of increasing thyroid activity, not only in tachycardia,

sweating, and nervousness, but also in rises of SPI, without change of the dose of thiourea which had previously been effective. With subsidence of symptoms, SPI sometimes (see, for example, B2143) fell in spite of a reduction in the dose of the drug. Whether SPI could have been reduced by larger doses of thiourea while the febrile complication persisted was not tested in most cases out of concern lest the drug be the cause of the disorder. In 2 of the fatal cases, B99489 and C11918, this course did result in reduction of SPI. In other cases interruption of therapy repeatedly led to rapid exacerbation. The sequence of events suggested not that the patients had become insensitive to the effects of the thio-drugs, but that the febrile complication had aggravated the hyperthyroidism, thereby causing SPI to rise.

This effect appears not to be peculiar to the particular type of febrile complication under discussion. It occurred also in response to intercurrent respiratory or urinary tract infections. The significance of the rises of SPI in terms of thyroid activity was sometimes hard to evaluate. At their onset they were not consistently paralleled by basal metabolism and resting pulse. At their height, fever and other symptoms confused efforts at analysis. Serum cholesterol usually proved to be within normal limits or low, never high. In most instances the clinical pictures were indicative of hyperthyroidism. On the whole the fluctuations of SPI, though not quantitatively proportional to other evidences of variation of thyroid activity, seemed clinically plausible.

In a few instances, however, changes of SPI of an altogether different order of magnitude were encountered. The most striking example is the sudden rise to 71.5 γ per cent in B2143. Figures of this magnitude have not been observed with even the most severe hyperthyroidism. They ordinarily denote that the subject has recently received an injection of some organic iodine compound, such as diodrast or priodax, that combines with the serum proteins. A less extreme example of the same phenomenon was observed in B54264 whose SPI rose to 46.0 γ per cent. Apparently, in a certain number of patients who have received thio-drugs for considerable periods, high concentrations of SPI may occur that are not related to thyroid activity. This anomaly does not appear to have any direct relation to the febrile complications, although it has been seen most frequently in patients with these complications. These points are well illustrated by Case B88761, a woman of 72, who was first seen in October, 1946, with obvious hyperthyroidism and heart failure, a basal metabolism of +27, and SPI 11.1 γ per cent. On 15 drops of Lugol's solution and 210 mg. of thiourea,

together with digitalis, she responded promptly, the symptoms disappearing and SPI falling to 6.9 γ per cent by November 6. At this time the dose of thiourea was reduced to 70 mg. By February, 1947, the SPI had risen to 9.7 γ per cent with some return of hyperthyroid symptoms. Two months later, with frank hyperthyroidism, the SPI was 12.1 γ per cent. The dose of thiourea was, therefore, increased to 140 mg. daily. On this regime she improved and seemed to maintain a euthyroid state throughout the spring and summer. In October, however, she noticed rapid gain of weight, somnolence, and other signs of retardation. On October 29 she appeared hypothyroid with SPI of 4.8 γ per cent. Thiourea was discontinued too long and by December she was overactive again with SPI 10.1 γ per cent. This time she was given only 70 mg. of thiourea daily. Symptoms and signs disappeared on this small dose. In May she was in excellent condition with SPI 6.3 γ per cent. She continued in this euthyroid state until October, when again she noted increase of weight and retardation. This time, however, her voice also became deeper and she became mentally confused. When seen October 27, she had all the symptoms and signs of myxedema, together with heart failure. Her serum cholesterol, which had previously been 233 mg. per cent, had risen to 394. Her SPI, however, was 10.8 γ per cent, a hyperthyroid value. The thiourea was discontinued and she was given first 0.06 and later 0.03 gm. of thyroid daily. Improvement was striking and immediate. November 1 cholesterol had fallen to 309 mg. per cent, while SPI had risen to 20.8 γ per cent. November 10, when she seemed euthyroid, they were, respectively, 242 and 22.5. November 19 SPI was 17.8 γ per cent. November 24 thyroid was discontinued and January 7, 1949, she was given 100 mg. of propylthiouracil daily. March 18, 1949, she was seen again, feeling well, cholesterol 299 mg. per cent, SPI 8.5 γ per cent. The impression was that the thyroid might be slightly hyperactive; at least her appearance did not suggest myxedema. The significance of these peculiarly high values of SPI is not clear. Obviously, when they occur, SPI no longer can serve as a measure of thyroid activity. The most plausible explanation is that some abnormal compound is formed under the influence of the thio-drug which behaves chemically like the circulating thyroid hormone. The circumstances surrounding the appearance of the phenomenon suggest that it is not altogether unrelated to thyroid activity. The extremely high value of 71.5 γ per cent in B2143 occurred during a hyperthyroid phase. SPI fell during recovery, but in correspondingly gigantic steps. The SPI of the myxedematous patient increased under the influence of thyroid from 10 to 20 and 22 γ per cent, an increment of 10

to 12, instead of the usual 1 to 3 γ per cent. The effect of this rise in terms of signs and symptoms of thyroid activity, including fall of serum cholesterol, was no greater than that of the small rise that usually attends correction of the hyperthyroid state. Whatever the cause or nature of these spuriously high iodine values may be, they appear to be transitory. In the subsequent course of B2143, with the establishment and maintenance of a relatively steady euthyroid state, SPI fell to 6.0 γ per cent. B88761, in a state of euthyroidism or mild hyperthyroidism, at the last observation, had a SPI of 8.5 γ per cent, distinctly lower than the figure of 10.8 γ per cent found 4 months earlier, when she was obviously myxedematous. The association of these specious values with the administration of thio-drugs may be merely coincidental. SPI has been measured more frequently in patients receiving thio-drugs than in any other group. In a large body of data from normals and patients with a great variety of diseases, however, no discrepancies of similar magnitude between SPI and other criteria of thyroid activity have been encountered. They do not appear to have any direct connection with toxic effects of thio-drugs or the febrile episodes that have been described, since B88761 had no evidences of either.

As yet no explanation for the phenomenon can be offered. One can speculate that the serum proteins may form some peculiarly stable compound with iodine or with the thyroid hormone, or that the ability of the tissues to utilize the hormone may be impaired. Neither explanation is satisfactory. The problem is under investigation. It must not be inferred that these misleading values occur frequently. The conviction remains that SPI is the most reliable single criterion of thyroid activity. High values that can be declared certainly spurious have been extremely rare, even among patients who have received thio-drugs. Their low and capricious incidence, indeed, will be the greatest obstacle to their elucidation.

Some other points about the reactions of these patients with febrile complications may be worth mentioning. A significant proportion during these episodes have had some evidences of impairment of liver function. This was especially prominent in B90726. Several of the others had slightly positive cholesterol flocculation tests and increases of cholesterol ratios (free : total cholesterol) to 0.33 and 0.35 instead of the normal 0.24 to 0.32. In addition, fatty acids of neutral fat exceeded 6 mM. per liter in many instances. Such disturbances of lipid patterns do not occur in uncomplicated thyroid disease; they usually betoken an accompanying hepatic disorder. Disturbances of carbohydrate metabolism, in one instance amounting to the

development of true diabetes, were notably frequent, but can not be considered statistically significant.

In spite of the time spent in description and discussion of these cases, a satisfactory assessment of the responsibility of thiourea is impossible, even in the 5 fatal cases. Two of the latter did have vascular lesions and one had skin lesions of types that there is reason to believe may be produced by drugs and other substances that can provoke allergic phenomena. Marine and Baumann[80] reported the occurrence of periarteritis nodosa in 2 rats after administration of thiourea. As they pointed out, however, the incidence was no higher than that of spontaneous periarteritis nodosa in other reported series of rats. Most of the other patients had symptoms and signs suggestive of kindred disorders. The constitution of the group, however, was peculiar and the incidence among them of such disorders, had they not received thiourea, is unpredictable. While responsibility can not be fixed unreservedly upon thiourea, the drug must be held suspect of complicity in a certain proportion of the cases. They have been presented *in extenso* in the hope that more attention will be given to the incidence in hyperthyroidism of such conditions and their relation to treatment with thio-drugs. If all these disorders are laid at the door of thiourea or thio-drugs, medical treatment of hyperthyroidism is not thereby discredited. The only conclusions to be drawn from this study to date might be that elderly or aged patients with evidences of vascular disease and with hyperthyroidism that can not be controlled over long periods by large doses of thio-drugs, may develop serious febrile illnesses associated with arthritis and peculiar lesions of the skin that may indicate or compel alteration or interruption of the treatment. They may, therefore, be regarded as unfavorable subjects for this type of therapy. Since the same patients make up the worst operative risks, the physician is left with Hobson's choice.

Conclusions

Of approximately 300 patients who have been treated for hyperthyroidism with thiourea, 35 while under therapy developed signs or symptoms of some kind that aroused suspicions of intoxication from the drug. The drug could be clearly incriminated in 6 cases, as clearly exonerated in 17. Neither agranulocytosis nor pathological leucopenia occurred in the series. One patient developed urticaria definitely referable to the drug after continuous treatment with small doses for 22 months. Three patients had febrile reactions within the first 2 weeks. In 2 the drug was discontinued because it provoked nausea. The main body of the paper is devoted to the discussion

of the significance of febrile reactions with various joint and skin manifestations that complicated the course of the remaining 12 patients. Five of these died and came to autopsy.

In a few instances the SPI of patients who had been treated for long periods with thio-drugs rose to concentrations that were quite out of keeping with the state of thyroid activity.

References

1 Astwood, E. B.: J. Pharm. Exp. Ther., 1943, *78,* 79.
2 Astwood, E. B.: J. Am. M. Ass., 1943, *122,* 78.
3 Astwood, E. B.: J. Clin. Endocr., 1945, *5,* 345.
4 Astwood, E. B., Bissell, A., and Hughes, A. M.: Endocrinology, 1945, *37,* 456.
5 Astwood, E. B., Sullivan, J., Bissell, A., and Tyslowitz, R.: Endocrinology, 1943, *32,* 210.
6 Astwood, E. B. and Vander Laan, W. P.: J. Clin. Endocr., 1945, *5,* 424.
7 Barfred, A.: Am. J. M. Sci., 1947, *214,* 349.
8 Barr, D. P. and Shorr, E.: Ann. Int. M., 1945, *23,* 754.
9 Bartels, E. C.: Ann. Int. M., 1945, *22,* 365.
10 Bartels, E. C.: J. Am. M. Ass., 1945, *129,* 932.
11 Danowski, T. S.: J. Biol. Chem., 1944, *152,* 201.
12 Danowski, T. S.: J. Biol. Chem., 1944, *152,* 207.
13 Danowski, T. S., Man, E. B., and Winkler, A. W.: Am. J. M. Sci., 1945, *210,* 777.
14 Danowski, T. S., Man, E. B., and Winkler, A. W.: Endocrinology, 1946, *38,* 230.
15 Danowski, T. S., Man, E. B., and Winkler, A. W.: J. Clin. Invest., 1946, *25,* 597.
16 Dieke, S. H., Allen, G. S., and Richter, C. P.: J. Pharm. Exp. Ther., 1947, *90,* 260.
17 Dieke, S. H. and Richter, C. P.: J. Pharm. Exp. Ther., 1945, *83,* 195.
18 DuBois, K. P. and Erway, W. F.: J. Biol. Chem., 1946, *65,* 711.
19 Eaton, J. C.: Lancet, 1945, *1,* 171.
20 Frisk, A. R.: Acta med. scand., 1947, *129,* 164.
21 Gabrilove, J. L., Kert, M. J., and Soffer, L. J.: Ann. Int. M., 1945, *23,* 537.
22 Griesbach, W. E., Kennedy, T. H., and Purves, H. D.: Nature, Lond., 1944, *154,* 610.
23 Himsworth, H. P., Morgans, M. E., and Trotter, W. R.: Lancet, 1947, *1,* 241.
24 Lahey, F. H. and Bartels, E. C.: Ann. Surg., 1947, *125,* 572.
25 Lahey, F. H., Bartels, E. C., Warren, S., and Meissner, W. A.: Surg., Gyn., Obst., 1945, *81,* 425.
26 Lundbaek, K.: Acta med. scand., 1946, *124,* 266.
27 McCullagh, E. P., Hibbs, R. E., and Schneider, R. W.: Am. J. M. Sci., 1947, *214,* 545.
28 Mackenzie, J. B. and Mackenzie, C. G.: Proc. Soc. Exp. Biol., N.Y., 1943, *54,* 34.
29 Man, E. B., Smirnow, A. E., Gildea, E. F., and Peters, J. P.: J. Clin. Invest., 1942, *21,* 773.
30 Marine, D. and Baumann, E. J.: Arch. Path., Chic., 1945, *39,* 325.
31 Marshall, E. K., Jr. and Davis, D. M.: J. Biol. Chem., 1918, *18,* 53.
32 Moore, F. D.: J. Am. M. Ass., 1946, *130,* 315.
33 Morgans, M. E.: Lancet, 1947, *1,* 519.

34 Palmer, M. V.: Ann. Int. M., 1945, *22,* 335.
35 Purple, M. R.: Thesis, Yale University School of Medicine, 1937.
36 Rawson, R. W., Moore, F. D., Peacock, W., Means, J. H., Cope, O., and Riddell, C. B.: J. Clin. Invest. 1945, *24,* 869.
37 Reveno, W. S.: J. Am. M. Ass., 1944, *126,* 153.
38 Reveno, W. S.: J. Am. M. Ass., 1947, *133,* 1190.
39 Ritchie, F. L. and Geddes, B. L.: Med. J. Australia, 1944, *1,* 381.
40 Selvaag, O.: Nord. med., 1948, *37,* 375.
41 Van Winkle, W., Jr., Hardy, S. M., Hazel, G. R., Hines, D. C., Newcomer, H. S., Sharp, E. A., and Sisk, W. N.: J. Am. M. Ass., 1946, *130,* 343.
42 Watson, E. M.: J. Clin. Endocr., 1945, *5,* 273.
43 Williams, R. H.: Arch. Int. M., 1947, *80,* 11.
44 Williams, R. H. and Clute, H. M.: N. England J. M., 1944, *230,* 657.
45 Williams, R. H., Clute, H. M., Anglem, T. J., and Kenney, F. R.: Endocrinology, 1946, *6,* 23.
46 Williams, R. H. and Frame, E. G.: Bull. Johns Hopkins Hosp., 1945, *77,* 314.
47 Winkler, A. W., Man, E. B., and Danowski, T. S.: J. Clin. Invest., 1947, *26,* 446.

NEWS AND COMMENT

The following comments are published here in recognition of the serious problems now facing premedical students and their faculty advisers, as well as the admission committees of the various medical schools.

Premedical Advisory Committee of Yale College

The increasing number of men in the University interested in premedical work (nearly two hundred in the freshman class) is responsible for the formation of a new committee to consider student and faculty problems associated with various phases of their training.

The University committee appointed by Dean DeVane includes Dr. J. W. Ewell of the Department of Health, Dr. P. S. Burnham of the Department of Psychology, Dr. R. B. Setlow of the Department of Physics, Dr. H. C. Thomas of the Department of Chemistry, and Dr. G. A. Baitsell of the Department of Zoology (Chairman).

The work of the committee naturally divides itself into four main fields:

1. Premedical club activities in charge of Dr. Ewell. With greatly increased numbers of college students enrolled as premedical candidates, the need for an agency devoted to their interests appeared urgent; and students with an interest in learning about medicine as a career have banded together as the Yale Premedical Association. The principal activity of this organization has been fairly frequent meetings with doctors as guest speakers; in the fall of the year, the gatherings have been devoted largely to the visiting representatives of medical college admission boards.

2. Medical aptitude tests in charge of Dr. Burnham. In October, 135 undergraduates who hope to enter some medical school in September, 1950, took the Medical College Admission Test in an all-day session in Woolsey Hall. Scores will be available to medical colleges only and will be useful in supplementing other criteria of admission, such as college records, recommendations, etc.

3. Procedure with reference to recommendations to medical schools in order to insure admission of the most promising candidates. What is, and what should be, the value of departmental recommendations?

4. Consideration of general problems associated with premedical training in the University.

(a) Generally speaking, the candidates majoring in one of the natural sciences are no longer given preferential treatment by admitting officers of medical schools. As a result, there is a marked tendency for premedical students to take only the minimum requirements in biology, chemistry, and physics, and to complete their major in fields that are less difficult and time

consuming. In this they are encouraged by the "broad training" statements of many medical schools. Certain questions may be raised here, such as:

After one year of work in a department, does the instructor know the man better than an Admitting Officer with a half-hour interview?

After two years in departmental courses, have we measured the man so that we would be satisfied to have him treat us in a major illness?

After three years, do we know with a fair chance the men who will make good in training and practice?

If the answer to these questions is not in the affirmative, it ought to be, and adequate measures should be taken to make it so.

(b) The Divisional Majors programs recently established in the Yale College curriculum offer a wide variety of inter-departmental choices and, typically, in none of these requirements is a student required to reach an "expert status" by mastering advanced courses and by testing with comprehensive examinations. Are these "majors" producing strong men—or are the men strong in spite of it?

(c) The development and selection of the courses in the various science departments, which are of the highest value for men headed toward medical training, and the integration of these and other courses into a unified curriculum which will give the highest values for acceptance of Yale students by medical schools and even more important, the highest values for a well-rounded education.

JOHN W. EWELL
PAUL S. BURNHAM
GEORGE A. BAITSELL
JOHN S. NICHOLAS

Choice of College Courses

Inquiries as to certain aspects of premedical training are frequently received by the School of Medicine from college advisers. The questions usually do not relate to minimum requirements for admission to our School; these courses of study are set forth in the catalogue and are in general the preparatory courses required by most medical schools. Rather, information is sought regarding the broader problem of the basic aim in premedical training. Below are presented two questions which are frequently asked, together with answers attempting to summarize the recent consensus of the Committee on Admissions.

Once premedical requirements have been met, to what subjects should the college student devote his remaining time? A limited number of advanced courses in chemistry, biology, and physics is useful. However, it is to be hoped that the future doctor has discovered or can anticipate the advantages to himself of a wider education. Every student should have a chance to study Shakespeare as well as solutions. Each individual must

choose for himself, but he will do well to remember that his ability as a doctor is not likely to be in proportion to the number of his premedical science courses and that the satisfactions of a medical life need not be limited to medicine.

What subject should be chosen as the major field? It is certainly to be hoped that the student will pursue his major interest. Provided that admission requirements are met, the field of concentration does not have to be a premedical subject. A "major" in philosophy or literature or history is not a barrier to admission to this School.

It is urged, then, that "premedical training" be thoughtfully and widely defined. The prospective applicant and his advisers should search for a means for his broad mental development. Such a program will include required prescribed training but will extend in addition to those fields, scientific or not, which promise full intellectual satisfaction and growth.

THOMAS R. FORBES

Selection of Medical Students

During the academic year 1948-1949 four individuals competed for each place for an entering freshman in the medical schools of the United States. Since nearly all of these persons filed applications at several institutions, the number of cases to be evaluated by Committees on Admissions was very large. The Yale University School of Medicine, for example, admitting 65 persons in its entering class, received more than 1,500 applications. Such figures are cited as an indication of the difficult problems of applicants and of admissions boards.

At this School, selection is accomplished by a method of repeated screening. As soon as possible after a completed application is received it is carefully examined. If the applicant's academic record, recommendations, and other qualifications do not all meet a fairly high standard, the application is promptly rejected. If, on the other hand, the qualifications appear excellent, the applicant is asked to come to New Haven for an interview, or, if the distance involved is excessive, he is interviewed by a regional representative of the School. If the Chairman of the Committee on Admissions has any doubts as to a particular application, it is studied by the remaining five members of the Committee, and a vote as to action on the application (reject, hold, interview) is taken. Applicants are usually interviewed by three members of the Committee. Subsequently, the interviews are discussed by the Committee, and a final vote is taken as to whether the applicant should be accepted. More than 200 applicants were interviewed during the past year.

The principal criteria for admission are the applicant's academic record, the opinions of his teachers and others, his performance in such examinations as the Medical College Admissions Test, the apparent adequacy of his health and finances, and his personality, interests, maturity, and ambitions. Here, of course, is the difficulty; in terms of desirability for medical school

the scores in paper records are certainly not infallible, and in the evaluation of personal qualities even less precision is possible. Each member of the Committee must strive to appreciate his responsibility to the School, to the applicants, and to the community, and then act in accordance with his best judgment. At present the large majority of applicants must necessarily be disappointed, but all of them may be assured that they have been carefully considered.

THOMAS R. FORBES

EVENTS

BEAUMONT CLUB

October 21, 1949

GRAVEYARD PEDIATRICS

E. J. CAULFIELD, M.D.

HARTFORD, CONNECTICUT

Dr. Caulfield's hobby of visiting and photographing old New England cemeteries led him to several interesting epidemiological studies. The old custom of sometimes referring to the cause of death on the headstones revealed the coincidence of many deaths among the children of various families at approximately the same time. From the assembled figures Dr. Caulfield was able to plot the extent and duration of several epidemics of diphtheria and bacillary dysentery. He has also accumulated interesting statistics on the number of multiple births and the number of maternal deaths in childbirth.

W.F.S.

THE RISE OF SCIENTIFIC ACTIVITY IN COLONIAL NEW ENGLAND

FREDERICK G. KILGOUR

(see page 123)

YALE MEDICAL SOCIETY

October 27, 1949

Woodward Lecture

SOME RECENT WORK ON COLDS AND INFLUENZA

BY

CHRISTOPHER HOWARD ANDREWS, M.D., F.R.S.

HEAD OF THE DEPARTMENT OF BACTERIOLOGY AND VIRUS RESEARCH

NATIONAL INSTITUTE FOR MEDICAL RESEARCH

HAMPSTEAD, ENGLAND

An account was given of the accomplishments of the new organization for the study of the epidemiology of influenza on a world-wide basis. There

was particular mention of the latest epidemic due to influenza virus A' originating in Sardinia in September, 1948, and spreading north through Western Europe during that winter.

The discussion of recent work on a few strains of the common cold virus centered upon the experiments carried out with human volunteers in a special research hospital in Salisbury, England. Methods used and the most interesting findings were described: the variations in clinical symptoms, the undetermined (perhaps negative) effect of chilling, the likely mode of spread—by manual contact, and some physical properties of the virus, or viruses, responsible. Attempts to infect and use any laboratory animals for the studies have failed.

MARY WHEATLAND

PUBLICATIONS FROM THE SCHOOL OF MEDICINE

ADAMS, ELIJAH: Observations of the influence of the hypophysis and adrenal cortex on blood platelet levels. Blood, N.Y., 1949, *4,* 936. From the Department of Physiological Chemistry.

BAIRD, H. W.: The duration of immunity to tetanus. Yale J. Biol., 1949, *21,* 385. From Department of Bacteriology and Immunology. Part of Thesis for M.D.

BLOOMER, W. E., HARRISON, W., LINDSKOG, G. E., AND LIEBOW, A. A.: Respiratory function and blood flow in the bronchial artery after ligation of the pulmonary artery. Am. J. Physiol., 1949, *157,* 317. From the Departments of Surgery and Pathology.

BLUMER, GEORGE: Brief recollections of the Yale Medical School (1906-1920). Yale J. Biol., 1949, *21,* 365.

BURR, H. S. AND MAURO, A.: Electrostatic fields of the sciatic nerve in the frog. Yale J. Biol., 1949, *21,* 455. From the Section of Neuro-Anatomy.

BURR, H. S. AND MAURO, A.: Millivoltmeters. Yale J. Biol., 1949, *21,* 249. From the Section of Neuro-Anatomy.

CANFIELD, NORTON: Trauma from noise in industry. J. Connecticut M. Soc., 1949, *13,* 21. From Division of Otolaryngology, Department of Surgery.

CHANG, H. T. AND RUCH, T. C.: Spinal origin of the ventral supraoptic decussation (Gudden's commissure) in the spider monkey. J. Anat., 1949, *83,* 1. From the Laboratory of Physiology. Part of Thesis for Ph.D.

COLBERT, J. W., JR.: Review of animal experimentation in infectious hepatitis and in serum hepatitis. Yale J. Biol., 1949, *21,* 335. From the Department of Internal Medicine.

DARLING, G. B.: The place of Yale Medical School in Connecticut medicine. J. Connecticut M. Soc., 1949, *13,* 649. Presented at the 157th Annual Meeting of the Connecticut State Medical Society, New Britain, May 4, 1949.

DEKKER, C. A., TAYLOR, S. P., JR., AND FRUTON, J. S.: Synthesis of peptides of methionine and their cleavage by proteolytic enzymes. J. Biol. Chem., 1949, *180,* 155. From the Department of Physiological Chemistry.

DOWNIE, G. R. AND CLIFTON, E. E.: A method for assay of serum proteolytic activity. Proc. Soc. Exp. Biol., N.Y., 1949, *71,* 138. From the Department of Surgery (Oncology).

DURAN-REYNALS, M. L. AND WINSLOW, C.-E. A.: Translation of: Regiment de Preservacio a epidimia o pestilencia e mortaldats by Jacme d'Agramont. Bull. Hist. M., 1949, *23,* 57. From the Department of Bacteriology and the School of Public Health.

ELKINGTON, J. R., TARAIL, ROBERT, AND PETERS, J. P.: Transfers of potassium in renal insufficiency. J. Clin. Invest., 1949, *28,* 378. From the Department of Internal Medicine.

EVANS, A. S. AND MELNICK, J. L.: Electron microscope studies of the vescicle and spinal fluids from a case of herpes zoster. Proc. Soc. Exp. Biol., N.Y., 1949, *71,* 283. From the Section of Preventive Medicine.

EVANS, T. S.: Progress in hematology. J. Connecticut M. Soc., 1949, *13,* 125.

FORBES, T. R.: A. A. Berthold and the first endocrine experiment: Some speculation as to its origin. Bull. Hist. M., 1949, *23,* 263. Read before Beaumont Club, Yale University School of Medicine, 13 May 1949.

FULDNER, R. V. AND SPEKTER, LOUIS: Cerebral palsy in Connecticut today. J. Connecticut M. Soc., 1949, *13,* 12.

FULTON, J. F.: A prolegomenon to the sciences. Isis, 1949, *40,* 99. Presidential Address: History of Science Society. New York City, 30 December 1948.

GIARMAN, N. J.: Antibiotic lactones and synthetic analogs II: Cardiotonic effects on the isolated frog heart. J. Pharm. Exp. Ther., 1949, *96,* 119. From the Department of Pharmacology.

GOODYER, A. V. N., PETERSON, E. R., AND RELMAN, A. S.: Some effects of albumin infusions on renal function and electrolyte excretion in normal man. J. Appl. Physiol., 1949, *1,* 671. From the Department of Internal Medicine.

GREEN, R. H.: Inhibition of multiplication of influenza virus by extracts of tea. Proc. Soc. Exp. Biol., N.Y., 1949, *71,* 84. From Department of Internal Medicine.

HALL, C. A., FRAME, BOY, AND DRILL, V. A.: Renal excretion of water and antidiuretic substances in patients with hepatic cirrhoses and rats with dietary liver injury. Endocrinology, 1949, *44,* 76. From the Department of Pharmacology.

HOOKER, C. W. AND FORBES, T. R.: Specificity of the intrauterine test for progesterone. Endocrinology, 1949, *45,* 71. From the Department of Anatomy.

HOOKER, C. W. AND FORBES, T. R.: The transport of progesterone in the blood. Endocrinology, 1949, *44,* 61. From the Department of Anatomy.

HOVENANIAN, M. S.: Massive non-filarial genital elephantiasis: Report of an unusual case. J. Connecticut M. Soc., 1949, *13,* 642. From the Section of Urology, Department of Surgery.

JORDAN, R. H.: Bronchopulmonary segments and their relation to disease. J. Connecticut M. Soc., 1949, *13,* 424. From the Department of Medicine.

KERSHAW, B. B.: Studies on the origin and development of normal hemagglutinins. Yale J. Biol., *21,* 463. From the Department of Bacteriology. Part of Thesis for Ph.D.

KLATSKIN, GERALD AND YESNER, RAYMOND: Factors in the treatment of Laennec's cirrhosis. I. Clinical and histological changes observed during a control period of bed-rest, alcohol withdrawal, and a minimal basic diet. J. Clin. Invest., 1949, *28,* 723. From the Department of Internal Medicine.

LEISE, J. M.: The relationship between pH tolerance, virulence, and proteolytic enzymes in bacteria. I. *Bacillus Anthracis.* Yale J. Biol., 1949, *21,* 233. From the Department of Bacteriology. Part of Ph.D. thesis.

LEISE, J. M.: The relationship between pH tolerance, virulence, and proteolytic enzymes in bacteria. II. Shigella. Yale J. Biol., 1949, *21,* 313. From the Department of Bacteriology. Part of thesis for Ph.D.

LEMPKE, R. E. AND SHUMACKER, H. B., JR.: Studies in experimental frostbite. III. An evaluation of several methods for early treatment. Yale J. Biol., 1949, *21,* 321. From the Department of Surgery.

LEMPKE, R. E. AND SHUMACKER, H. B., JR.: Studies in experimental frostbite. IV. The response of the sympathetically denervated extremity to freezing. Yale J. Biol., 1949, *21,* 401. From the Department of Surgery.

LI, MIN HSIN AND GARDNER, W. U.: Further studies on the pathogenesis of ovarian tumors in mice. Cancer Res., 1949, *9,* 35. From the Department of Anatomy.

LIAO, SUNG J.: The agglutination of autoclaved hemolytic streptococci by serum from patients with rheumatic fever and other conditions. J. Clin. Invest., 1949, *28,* 331. From the Section of Preventive Medicine.

LIVINGSTON, R. B.: A journey of lepers on Okinawa. Yale J. Biol., 1949, *21,* 449.

LOWMAN, R. M., WATERS, L. L., AND MENDELSOHN, WILLIAM: Intussuseption associated with small bowel tumors. J. Connecticut M. Soc., 1949, *13,* 327. From the Department of Radiology, Department of Pathology, and The Tumor Clinic, Grace-New Haven Community Hospital, Grace Unit.

MARVIN, H. M.: Differential diagnosis of coronary artery disease. J. Connecticut M. Soc., 1949, *13,* 186. From the Department of Medicine.

MATHEWS, F. P.: Poliomyelitis epidemic, possibly milk-borne, in a naval station, Portland, Oregon. Am. J. Hyg., 1949, *49,* 1. From the Department of Public Health.

MAURO, A. AND BARRON, D. H.: Instrumentation for laboratory exercises in basic electrophysiology. Yale J. Biol., 1949, *21,* 305. From the Section of Neuro-Anatomy and the Laboratory of Physiology.

MAYER, J.: Gross efficiency of growth of the rat as a simple mathematical function of time. Yale J. Biol., 1949, *21,* 415. From the Yale Nutritional Laboratory, Department of Physiological Chemistry.

MELNICK, J. L.: Isolation of poliomyelitis virus from single species of flies collected during an urban epidemic. Am. J. Hyg., 1949, *49,* 8. From the Section of Preventive Medicine.

MELNICK, J. L., SHAW, E. W. AND CURNEN, E. C.: A virus isolated from patients diagnosed as non-paralytic poliomyelitis or aseptic meningitis. Proc. Soc. Exper. Biol., N.Y., 1949, *71,* 344. From the Section of Preventive Medicine and Department of Pediatrics.

NAHUM, L. H., CHERNOFF, H. M., AND KAUFMAN, W.: Spread of excitation in the dog's heart. Am. J. Physiol., 1949, *157,* 248. From the Laboratory of Physiology.

NISSEN, H. W. AND RIESEN, A. H.: Onset of ossification in the epiphyses and short bones of the extremities in chimpanzee. Growth, 1949, *13,* 45. From the Department of Zoology, Yale Univ. & Yerkes Lab. of Primate Biology.

OPSAHL, J. C.: The influence of hormones from the adrenal cortex on the dermal spread of India ink with and without hyaluronidase: Preliminary report. Yale J. Biol., 1949, *21,* 255. From the Department of Bacteriology. Ph.D. Thesis.

OPSAHL, J. C.: Elevated environmental temperature: Its possible influence on the action of spreading factor. Yale J. Biol., 1949, *21,* 433. From the Department of Bacteriology. Part of thesis for Ph.D.

OPSAHL, J. C.: Dermal spreading of India ink with and without hyaluronidase as influenced by hormones from the adrenal cortex. Yale J. Biol., 1949, *21,* 487. From the Department of Bacteriology. Part of thesis for Ph.D.

OTTKE, R. C.: The occurence of ergosterol in *Neurospora crassa.* Arch. Biochem., N.Y., 1949, *23,* 49. From the Department of Botany and Microbiology.

PFEIFFER, C. A.: Effects of bone extracts injected into the mouse testis. Proc. Soc. Exp. Biol., N.Y., 1949, *71,* 388. From the Department of Anatomy.

PINCHOT, G. B., CLOSE, V. P., AND LONG, C. N. H.: Adrenal changes produced in rats by infection with B. tularense and B. coli. Endocrinology, 1949, *45,* 135. From the Department of Physiological Chemistry.

POMPER, S. AND BURKHOLDER, P. R.: Studies on the biochemical genetics of yeast. Proc. Nat. Acad. Sci., 1949, *35,* 456. From the Osborn Botanical Laboratory, Yale University.

QUINN, R. W., WATKINS, J. H., AND QUINN, J. P.: Rheumatic heart disease in seventh and eighth grade Connecticut school children. J. Connecticut M. Soc., 1949, *13,* 515. From the Section of Preventive Medicine.

REAUME, S. E. AND TATUM, E. L.: Spontaneous and nitrogen mustard-induced deficiencies in *Saccharomyces cerevisiae*. Arch. Biochem., N.Y., 1949, *22*, 331. From the Department of Microbiology.

RELMAN, A. S., GOODYER, A. V. N., AND PETERSON, E. R.: Effect of mannitol on salt excretion during water diuresis. J. Appl. Physiol., 1949, *1*, 601. From the Department of Internal Medicine.

ROBERTS, SIDNEY AND WHITE, ABRAHAM: Studies on the origin of the serum proteins. J. Biol. Chem., 1949, *180*, 505. From the Department of Physiological Chemistry, Yale University, and the School of Medicine, University of California at Los Angeles.

RUSSELL, J. A. AND CAPPIELLO, MARJORIE: The effects of pituitary growth hormone on the metabolism of administered amino acids in nephrectomized rats. Endocrinology, 1949, *44*, 333. From the Department of Physiological Chemistry.

RUSSELL, J. A. AND CAPPIELLO, MARJORIE: The relationship of temperature and insulin dosage to the rise of plasma amino nitrogen in the eviscerated rat. Endocrinology, 1949, *44*, 127. From the Department of Physiological Chemistry.

SACHS, ERNEST, JR., BRENDLER, S. J., AND FULTON, J. F.: The orbital gyri. Brain, 1949, *72*, 227. From the Laboratory of Physiology.

SADUSK, J. F., JR.: The immunization of troops with typhus vaccine and the characteristics of typhus in immunized individuals. Yale J. Biol., 1949, *21*, 211. From the Department of Internal Medicine. Presented at a symposium on the Rickettsial Diseases of Man, American Association for the Advancement of Science.

SAUNDERS, R. H., JR.: Erythema multiforme exudativum: Report of a case with false-positive serology. Yale J. Biol., 1949, *21*, 481. From the Department of Internal Medicine.

SIMMONDS, SOFIA AND FRUTON, J. S.: The utilization of amino acids and peptides by mutant strains of *Escherichia coli*. J. Biol. Chem., 1949, *180*, 635. From the Osborn Botanical Laboratory and the Department of Physiological Chemistry.

SIMS, E. A. H.: Creatinuria from guanidoacetic acid ingestion and its relation to the site of action of methyl testosterone. Am. J. Physiol., 1949, *157*, 404. From the Department of Internal Medicine.

SMITH, F. W., GARDNER, W. U., LI, MIN HSIN AND KAPLAN, HARRY: Adrenal medullary tumors in mice. Cancer Res., 1949, *9*, 193. From the Department of Anatomy.

STRAUSS, M. J. AND SIGEL, HARRY: "Intraderm sulfur" in the treatment of acne vulgaris. J. Connecticut M. Soc., 1949, *13*, 100. From the Division of Dermatology.

STRONG, L. C.: A new theory of mutation and the origin of cancer. Yale J. Biol., 1949, *21*, 293. From the Department of Anatomy.

SWIFT, W. E., JR., AND BEARDSLEY, F. A.: The effect of a 42-day course of treatment on the sensitivity of the tubercle bacillus to streptomycin. J. Immun., Balt., 1949, *62,* 117. From the Department of Pharmacology.

SZEGO, C. M., AND WHITE, ABRAHAM: The influence of growth hormone on fasting metabolism. Endocrinology, 1949, *44,* 150. From the Department of Physiological Chemistry, Yale University, and the School of Medicine, University of California at Los Angeles.

TARAIL, ROBERT AND ELKINGTON, J. R.: Potassium deficiency and the role of the kidney in its production. J. Clin. Invest., 1949, *28,* 99. From the Department of Internal Medicine.

THOMS, HERBERT: Natural childbirth. J. Connecticut M. Soc., 1949, *13,* 47. From the Department of Obstetrics and Gynecology.

TRINKAUS, J. P.: The surface gel layer of fundulus eggs in relation to epiboly. Proc. Nat. Acad. Sci., 1949, *35,* 218. From the Osborn Zoological Laboratory, Yale University, and Marine Biological Laboratory.

YAKOVLEV, P. I.: Loss of consciousness and convulsions in middle-aged patients. J. Connecticut M. Soc., 1949, *13,* 521. From the Department of Psychiatry and Mental Hygiene.

YOUNG, L. E.: The extractable histamine content of gastric mucosa and lung before and after parenteral histamine administration. Yale J. Biol., 1949, *21,* 499. From the Department of Surgery.

BOOK REVIEWS

MANUAL OF HUMAN DISSECTION. By Edwin M. Shearer. Edited by Charles E. Tobin. Philadelphia, Blakiston and Company, 1949. xv, 286 pp. $4.50.

The second edition of Edwin M. Shearer's *Manual of Human Dissection* has been issued under the editorship of Charles E. Tobin, Ph.D., associate professor of anatomy at the University of Rochester. In a brief preface Doctor Tobin outlines the changes which have been made. To the reviewer these do not appear to have substantially altered the body of Shearer's original work. While the order of illustrations has been changed, their number remains the same. Comparison of the two editions shows that of the 79 drawings appearing in the original work, 75 have been carried over intact to the new edition. Two of the remaining four drawings are somewhat different views of regions illustrated in the original edition. Six sections of the text, selected at random, were compared in the two editions. The section treating of the prevertebral region has been extensively rewritten and enlarged, constituting a new treatment of the topic. In the two sections covering the peritoneum and the orbit a few emendations appear, as well as some changes in the dissection procedure. The remaining three sections—pectoral region, axilla, extensor region of forearm and hand—show but minor variations from the original text. Although the present edition does not run to as many pages as its predecessor, doubtless its more compact format has made possible the inclusion of additional dissection procedures, as mentioned by Doctor Tobin in his preface.

In its present form this book admirably fulfills Doctor Shearer's aim of furnishing a brief and practical guide to the dissector. The manual rests handily on the reading stand, and its printing is large enough to be seen from across the cadaver; bold face type stresses important names and relationships. In using the manual the student will have the benefit of brief and pertinent counsel from one who has quite evidently been over the ground, nor will he be burdened by the garrulity of an anatomical textbook. The black and white drawings possess the seemly virtue of resembling cadaver material more closely than the ofttimes stylized figures of the atlases. The manual can be recommended as an excellent guide for the beginning dissector. Those already in possession of the first edition may not find investment in the second a necessity.

RUSSELL V. FULDNER

INTRODUCTION TO THE SZONDI TEST. By Susan Peri. New York, Grune and Stratton, 1949. xiv + 354 pp. $5.00.

The Szondi Test is a projective technique based on the assumption that the subject's emotional response to photographs of persons with mental disorders depends on some sort of similarity between the psychodynamics of the subject and the person in the photograph. It is assumed that when the subject selects the pictures he likes or dislikes he is identifying with the

person in the photograph and thereby revealing his need-tension system. The pattern of needs so elicited is scored so as to produce a profile which allows the clinician to formulate the subject's psychodynamics. Susan Peri's *Introduction* deals mainly with the interpretation of the profile and formulation of the subject's psychodynamics, the theory having been dealt with previously by Szondi. She leans heavily on psychoanalytic jargon in her description of the profiles.

The Szondi Test, and therefore the formulations derived from its use, can only be valid if (1) it is true that a subject does identify himself with a photograph he chooses to like or dislike, and (2) that subjects do reliably interpret photographs to signify one emotional reaction or another. The evidence is to the contrary. It has been shown that a subject's liking or disliking a picture does not depend necessarily on his process of identification, and that subjects cannot reliably interpret the meaning of pictures portraying emotional reactions. The Szondi Test is, therefore, of doubtful validity.

The author claims as her purpose in writing the book the preparation of a manual which will make the test useful to clinicians. Certainly, the respectable clinician would demand above every other claim that the test be a valid and reliable instrument. The failure of the *Introduction* to provide this information leaves the clinician with an interesting, highly speculative test of doubtful validity. He cannot use it with the assurance that the interpretations are anything more than intuitive guesses as to the psychodynamics of the subject.

When the basic tenets of the Szondi Test have been demonstrated to be true and the interpretations valid, the clinician will welcome the facility with which he can formulate the patient's psychodynamics by this method. Until then, he will consider it only as an interesting procedure requiring a good deal of caution in its application.

H. E. ROSVOLD

BONE MARROW BIOPSY. HEMATOLOGY IN THE LIGHT OF STERNAL PUNCTURE. By S. J. Leitner. English translation revised and edited by C. J. C. Britton and E. Neumark. New York, Grune and Stratton, 1949. 421 pp. $8.50.

For those genuinely interested in hematology, this book should be a welcome acquisition. Dr. Leitner's contributions in this field have long been recognized outside of his native Switzerland. Actually the present volume is more than a translation, for the British writers, Britton and Neumark, have made use of the author's willingness to permit additions and alterations to the second Swiss edition.

One of the most impressive features of the book is the large number of references it contains. There are, for example, approximately 900 entries in the bibliography for the chapter on "Disorders of Erythropoiesis" and about 900 items in the bibliography for the chapter on "Disorders of Leukopoiesis." The bulk of the references are to the continental literature.

For the average reader in this country, this feature should be a welcome addition. There are scattered up-to-date references to the American literature and even more complete coverage of recent British papers. (Dr. Britton is co-author with L. E. H. Whitby of the well-known British text, *Disorders of the Blood.*)

Unfortunately the book is not easy reading. This is partly due to the commendable attempt of the writers to include references to a large volume of work by others. Actually much of the data mentioned is conflicting and the reader is apt to be left confused. Since science is filled with such contradictory conclusions, some of this is understandable and pardonable. Frequently, however, it is not clear where the present authors stand on certain controversial matters, what their own experience has been, or which group of investigators they feel is closest to the truth. Some of the work to which they refer appears to this reviewer to be so unreliable that it would seem better to have omitted the reference completely.

On the whole, the overall organization of the material is good, although some syndromes are described which are not recognized in this country and the classification of some dyscrasias would appear to be questionable. The authors are to be congratulated on the liberal number of concise case histories which they present with pertinent laboratory data. In fact the volume contains a great deal of clinical information outside the field of bone marrow study. The clinical descriptions of blood dyscrasias are not (and doubtless were not intended to be) as thorough and complete as those found in several texts in English on clinical hematology in general.

The format of the volume is good, the type very legible, the paper of high quality. Most of the illustrations are black and white reproductions of photomicrographs, but they are generally clear and pertinent. There are six colored plates.

DAVID H. CLEMENT

COMPARATIVE ANATOMY. By L. A. Adams and S. Eddy. New York, John Wiley and Sons Inc., 1949. vii + 520 pp. $5.00.

This book is a new arrangement and thorough revision of Professor Adams' earlier work, *Introduction to the Vertebrates.* The first part of the book discusses the general features which characterize the main groups of the vertebrates. The various theories that have been offered for the origin of the vertebrates are briefly given along with a consideration of phylogenetic relationships. A chapter is also devoted to comparing the pattern of development found in the different organ systems.

The major part of the book is given over to chapters dealing with the comparative study of the organ systems and their parts as found in each of the vertebrate groups. The material is well illustrated with 364 line drawings. There is a good index and a comprehensive glossary to aid the student being initiated to the basic principles of comparative anatomy.

L. S. STONE

FUNDAMENTALS OF INTERNAL MEDICINE. By Wallace M. Yater. 3d ed. New York, Appleton-Century-Crofts, Inc., 1949. xviii + 1451 pp. $12.00.

A textbook of medicine is usually intended to orient the beginning student in the fundamentals of the broad field of internal medicine. This book admirably fulfils this concept. The style and format make for easy reading. This edition has been enlarged from the previous one. Also, it has been generally brought up to date with recent advances, especially in the field of therapeutics. It seemed to the reviewer that none of the sections could be considered "weak" or especially inadequate for their purpose. The sections on heart disease, electrocardiography, and the endocrine glands were unusually well handled, authoritative, and sufficiently detailed. Also, it was surprising to find such an adequate section on the common dermatoses. Chapters on antibiotics and chemotherapeutic agents and on inhalation therapy have been added to this edition. The section on symptomatic and supportive treatment seemed pertinent since it involves a subject too often neglected in formal teaching.

The book is not without minor errors and misleading statements. Slight errors were present in the formulae for calculation of the mean corpuscular volume and mean corpuscular hemoglobin. The term "achrestic" was misspelled. Also, the sections on acidosis and alkalosis were presented too glibly for real accuracy. One was almost led to believe that the determination of the serum pH was necessary to make a diagnosis of acidosis or alkalosis. Little consideration was given to acidosis associated with high nor to alkalosis with low serum bicarbonate content. Diabetes mellitus is bluntly described as a disease wherein carbohydrate utilization is impaired because of an insufficient supply of insulin. Present knowledge would not warrant such a didactic definition. Occasionally, dubious statements are made; for example, that patients with "primary hypotension" are "especially vulnerable to pneumonia and less serious respiratory infections." Undoubtedly this statement was based on a personal impression rather than a documented fact.

The text is intended to give practical considerations to the essentials of general practice. While medicine can be, and frequently is, practiced by rules of thumb and while positive statements may be reassuring to the student, the omission of controversial and unsolved problems neither stimulates nor inspires the reader. While the omission can be cited as a definite criticism, this is not the only textbook of medicine to fall short in this regard. In any event, it is still clear that Dr. Yater has included more sound information than is usually found in one volume. The diagnostic charts, tables, and illustrations are well conceived and selected. For the beginning student and general practitioner the text will find wide use.

WILLIAM W. ENGSTROM

ESSAYS ON SEX. By H. M. Young. Boston, The Christopher Publishing House, 1949. 277 pp. $5.00.

This volume, presenting essays on social problems related to sex, brings together in book form material written by the late Dr. H. M. Young, an

eminent urologist who was deeply interested in the medical aspect of sex. It is dedicated "to troubled young people and their parents." It is by no means written for a lay audience, however, and should interest physicians as a fine exposition of sound and forward thinking in this field. The essential thesis of the work is to look at sex frankly and clearly so that it will appear in its proper proportion to a generation which seems to be having hesitancy and difficulty in accepting maturity and its responsibilities.

The material was originally presented in the form of editorials and this character fortunately has been preserved in the format of the book, an arrangement which adds greatly to its readability. It is edited by the author's wife, Maud H. Young, who aided him in the preparation of the material.

HERBERT THOMS

THE RAT IN LABORATORY INVESTIGATION. 2d ed. By Edmund J. Farris and John Q. Griffith, Jr. Philadelphia, J. B. Lippincott Company, 1949. 542 pp. $15.00.

The skillful organization and nature of the reference material contained in the original volume of this handbook have made unnecessary the revision of many of the chapters for the second edition. Accordingly the authors have published without change illustrations and descriptions of topics such as breeding, care, anatomy, hematology, and physiology as well as standard procedures for surgical, radiological, and psychological studies of the rat.

In the discussion of nutritional requirements it is disappointing that no attempt has been made to review the factors of the vitamin-B complex in the light of recent developments. A supplementary list of twenty new references has been added to the bibliography in lieu of revision of the chapter, but no citation of these papers occurs in the text.

The most valuable contribution of the present edition is the complete revision of the pages concerned with the action of pharmacological agents. Not only have the therapeutic and lethal dosages of many new drugs been recorded, but the form of the tabulated material is arranged for more convenient reading. Attention also should be directed to the improvements in the section dealing with the osseous system. Incorporated in the chapter are methods for study of calcification, measure of growth, content of phosphatase, and radioactive isotopes in bone.

This excellent manual remains the best available guide for all types of laboratory experimentation involving the rat as test animal.

EDITH G. FRY